NATIONAL TOXICOLOGY PROGRAM

FISCAL YEAR 1985

ANNUAL PLAN

NOTE: ALL FISCAL ASSUMPTIONS ARE BASED ON THE PRESIDENT'S PROPOSED FY 1985 BUDGET

DEPARTMENT OF HEALTH AND HUMAN SERVICES
U.S. PUBLIC HEALTH SERVICE

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NATIONAL TOXICOLOGY PROGRAM

ANNUAL PLAN
FOR
FISCAL YEAR 1985

National Cancer Institute/National Institutes of Health
National Institute of Environmental Health Sciences/National Institutes of Health
National Center for Toxicological Research/Food and Drug Administration
National Institute for Occupational Safety and Health/Centers for Disease Control

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National Toxicology Program

Public Health Service

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL TOXICOLOGY PROGRAM

Annual Plan for Fiscal Year 1985

TABLE OF CONTENTS

Executive Summary-- 1

Introduction--- 8

Resources and Planning Assumptions--- 11

Oversight and Review--- 16

Coordination and Communication--- 22

Organization--- 25

Toxicology Research and Testing Overview------------------------------------- 29

- Cellular and Genetic Toxicology---------------------------------- 34
- Carcinogenesis Research and Testing------------------------------ 94
- Toxicologic Characterization-------------------------------------128
  - The Benzidine-Dye Initiative--------------------------------138
  - Chemical Disposition---------------------------------------142
  - Chemical Pathology---154
  - Cutaneous Toxicology---------------------------------------168
  - Immunological Toxicology-----------------------------------171
  - Neurobehavioral Toxicology---------------------------------177
  - Pulmonary Toxicology---------------------------------------182
  - Safety Evaluations of Ortho Phthalic Acid Esters and Related Compounds-----------------------------------185
- Reproductive and Developmental Toxicology------------------------188

Coordinative Management Activities---199

- Chemical Nomination and Selection--------------------------------201
- Chemical and Laboratory Test Management--------------------------224
- Data Audits--226
- Chemistry Resources--229
- Chemical Respositories---237
- Laboratory Animal Resources--------------------------------------240
- Chemical Health and Safety---------------------------------------242
- Data Management and Analysis-------------------------------------244

Information Generation and Dissemination-------------------------------------251

Annual Report on Carcinogens---255

Appendix A - National Toxicology Program-Agency Contracts--------------------259

Appendix B - Bibliography-NTP Publications-FY 1984---------------------------267

Chemical Indexes---316

LIST OF TABLES

Table 1 Chemical Test Results for Mutagenicity in *Salmonella* Assays in FY 1984 ---- 63

Table 2 Chemicals Selected for Mutagenicity Testing in *Salmonella* in FY 1985 ---- 68

Table 3 Chemical Test Results for Heritable Genetic Effects in *Drosophila* in FY 1984 ---- 78

Table 4 Chemicals Selected to be Tested for Heritable Genetic Effects in *Drosophila* in FY 1985 ---- 79

Table 5 Chemical Test Results for Mutagenicity in L5178Y Mouse Lymphoma Cells in FY 1984 ---- 80

Table 6 Chemicals Selected to be Tested for Mutagenicity in L5178Y Mouse Lymphoma Cells in FY 1985 ---- 82

Table 7 Chemical Test Results for Cytogenetic Effects in Chinese Hamster Ovary Cells in FY 1984 ---- 85

Table 8 Chemicals Selected to be Tested for Cytogenetic Effects in Chinese Hamster Ovary Cells in FY 1985 ---- 87

Table 9 NTP Toxicology and Carcinogenesis Study Results ---- 98

Table 10 Chemicals in the Prechronic Phase of Toxicology and Carcinogenesis Studies at the End of FY 1984 ---- 104

Table 11 Chemicals in the Chronic Phase of Toxicology and Carcinogenesis Studies at the End of FY 1984 ---- 105

Table 12 Chemicals Scheduled to Start in the Prechronic Phase of Toxicology and Carcinogenesis Studies in FY 1985 ---- 114

Table 13 Chemicals Scheduled to Start in the Chronic Phase of Toxicology and Carcinogenesis Studies in FY 1985 ---- 116

Table 14 Chemicals for Which Toxicology and Carcinogenesis Studies Will Be Completed Through In-Life Phase in FY 1985 ---- 117

Table 15 Summary of the NTP Benzidine Congener Initiative ---- 140

Table 16 Chronic Studies Reviewed During FY 1984 ---- 163

Table 17 Completed Data Audit Reviews Through FY 1984 ---- 164

Table 18 Prechronic Studies Reviewed During FY 1984 ---- 166

LIST OF TABLES (Continued)

Table 19 Interim Sacrifice Studies Reviewed During FY 1984 ----- 167

Table 20 Core Panel for Detecting Chemical-Induced Immunotoxicity ----- 175

Table 21 Chemicals Assessed for Potential Immunological Alterations ----- 176

Table 22 Developmental Toxicity Studies Completed or in Progress in FY 1984 ----- 194

Table 23 Studies on the Fertility Assessment by Continuous Breeding Protocol for which a Final Report has been Completed ----- 195

Table 24 Chemicals Under Study in the Fertility Assessment by Continuous Breeding Protocol ----- 196

Table 25 Short-Term Reproductive Toxicity Assay Results ----- 197

Table 26 List of Chemicals Selected for FY 1984 Short-Term *In Vivo* Reproductive Toxicity Assay ----- 198

Table 27 NTP Chemical Nomination Elements ----- 207

Table 28 NTP Chemical Selection Principles ----- 209

Table 29 Chemicals Nominated for Extensive Toxicological Testing in FY 1984 ----- 210

Table 30 Testing Recommendations for Chemicals Reviewed by the NTP Chemical Evaluation Committee on November 8, 1983 ----- 215

Table 31 Testing Recommendations for Chemicals Reviewed by the NTP Chemical Evaluation Committee on February 24, 1984 ----- 218

Table 32 Testing Recommendations for Chemicals Reviewed by the NTP Board of Scientific Counselors on August 17, 1984 ----- 220

Table 33 NTP Fiscal Year 1984 Priority Chemicals for In-Depth Toxicological Evaluation ----- 223

Table 34 Chemicals Procured and Analyzed for Teratology Studies in FY 1984 ----- 232

Table 35 Chemicals Procured and Analyzed for Continuous Breeding Program FY 1984 ----- 233

Table 36 Chemicals Procured and/or Analyzed for Immunology Studies FY 1984 ----- 234

Table 37 Chemistry Resources Support for TRTP In-House Studies in FY 1984 ----- 235

Table 38 NIEHS/NTP Chemistry Laboratory Studies in FY 1984 ----- 236

Table 39 NTP Chemical Repository Holdings and Activities in FY 1984 ----- 239

LIST OF FIGURES

Figure 1 Agency Origin and Amounts of Funding------------------------------- 13

Figure 2 National Toxicology Program - Funding Levels by Program Activity - FY 1983-1985-- 14

Figure 3 National Toxicology Program - Funding Levels of Program Activities by Program Area - FY 1984-- 15

Figure 4 NTP Chemical Nomination and Selection Process---------------------206

EXECUTIVE SUMMARY
NATIONAL TOXICOLOGY PROGRAM
ANNUAL PLAN FOR FISCAL YEAR 1985

The National Toxicology Program (NTP) begins its seventh year in FY 1985. The Program was established by the Secretary, DHHS, in November 1978 to integrate DHHS activities and resources concerned with determining the toxicologic potential of chemicals, and to establish an effective dialogue between the health research and regulatory agencies, enabling stronger links between toxicology research and regulatory needs.

Four specific and overarching goals continue to: (1) broaden the spectrum of toxicologic information obtained on chemicals selected; (2) increase the numbers of chemicals tested within funding limits; (3) develop and validate a series of tests and protocols appropriate for regulatory needs; and (4) communicate plans and results to governmental agencies, the medical and scientific communities, and the public.

Over its six-year existence, in toxicology testing alone, the NTP's capabilities have evolved from a limited collection of routine individual testing activities to an integrated program studying chemicals for multiple endpoints using specially tailored protocols. During this time, the development, validation, and application of better, more specific, rapid and less expensive test methodologies have evolved as the core of NTP scientific activity.

Accomplishments for FY 1984 (highlighted below) and plans for FY 1985 are described in this FY 1985 Annual Plan. These are described separately by each contributing agency in the scientific and management sections. The name of an agency staff person is given as a contact for each project or program activity. A listing of program leaders and contact persons along with phone numbers and addresses appears in Appendix A. A bibliography of recent NTP-related publications, arranged alphabetically by the last name of the first author and by type of publication, is included in Appendix B. For the first time, to facilitate locating a particular project or activity, the largest chapter (Cellular and Genetic Toxicology) has its own table of contents.

Accomplishments of the NTP in FY 1984 Include:

Cellular and Genetic Toxicology

- Completed 396 chemical tests in genetic toxicology systems, including measurements of gene mutations in bacteria (*Salmonella*) and mammalian cells (mouse lymphoma), cytogenetic effects in mammalian cells (Chinese hamster ovary), and heritable genetic effects in fruit flies (*Drosophila*).

- Evaluated between 20 and 30 priority chemicals in each component assay of a coordinated cellular and genetic toxicology testing project to aid in setting priorities for long-term *in vivo* testing and to provide a more comprehensive data base for diverse groups of chemicals.

- Began a cross-species comparison of the capability of primary liver and bladder cells to activate precarcinogens of various chemical classes to mutagenic metabolites.

- Initiated the *Salmonella* assay to detect urinary mutagens from rats on

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prechronic and chronic studies.

- Continued development and validation of a dual laboratory evaluation of three mammalian cell transformation systems.

- Began evaluating the mouse erythrocyte micronucleus assay as an adjunct to to prechronic testing in rodents.

- Continued interagency collaboration on a project using the primary hepatocyte/DNA repair system to detect genotoxicity of chemicals.

- Obtained chromosomal aberration and sister chromatid exchange baseline data on more than 250 human subjects.

- Completed developmental work for *in situ* monitoring of mutagens in the workplace.

Carcinogenesis

- Completed peer review of the draft technical reports for 13 toxicology and carcinogenesis two-year studies including high-volume industrial chemicals such as benzene and 1,3-butadiene.

- Began in-life data audits of selected long-term toxicity studies.

- Continued refinement and application of short-term *in vivo* rodent liver tumor models for assessing initiation/promotion mechanisms of chemical carcinogenesis.

- Completed carcinogenesis assessment of several workplace substances in rodents finding two types of quartz carcinogenic, silica sand and substitutes cocarcinogenic, and topical asphalt fume condensates more carcinogenic than expected.

Toxicologic Characterization

- Initiated toxicologic characterization of chemicals under the Superfund Act, including chemical disposition, mutagenicity, fertility and reproductive testing, and chronic exposure toxicology studies.

- Completed chemical disposition and genetic toxicology studies on benzidine dyes while continuing two-year studies with selected dyes.

- Continued multidisciplinary studies on selected ortho phthalic acid esters, and began expanded toxicology and pharmacokinetic studies on 1,3-butadiene and two structural analogs.

- Began study on mechanisms of toxicity of metals as part of prechronic toxicity testing.

- Determined that 'dioxin' in contaminated soil is readily bioavailable after oral administration to rodents producing biological effects similar to those produced by the pure chemical.

- Continued development of test procedures for measuring absorption and toxicity after dermal administration of chemicals to aid design of *in vivo* toxicology studies.
- Completed laboratory studies on percutaneous absorption of benzene, toluene, carbon disulfide and ethyl benzene in support of workplace standards.
- Continued use of the immunotoxicology panel to assess altered host resistance and immunological impairment after chemical exposure.
- Continued development of automated procedures for measuring neurobehavioral toxicity using home cage behaviors.
- Completed a multi-species two-year inhalation exposure study of pulmonary and mutagenic effects of diesel exhaust and coal dust.
- Began study to evaluate effects of increasing age on the metabolism, disposition and toxicity of chemicals.
- Demonstrated stability and equivalent bioavailability of chemicals given orally to rodents in microencapsulated form.
- Developed and applied to workers or human volunteers methods for monitoring urine and blood concentrations of chemicals including ethylene glycol monoethyl ether, methylethyl ketone, toluene and xylene.

Reproductive and Developmental Toxicology

- Completed 13 teratology studies on eight chemicals with six other studies in progress.
- Continued using the short-term *in vivo* reproductive toxicity assay and sperm morphology/vaginal cytology assays to help set priorities for conventional teratology testing.
- Began evaluation of two cell culture systems as *in vitro* indicators of teratogenic potential.
- Performed evaluations of semen quality in two populations of workers occupationally exposed to ethylene dibromide.

Data Management and Analysis

- Collected, stored and processed in-life chronic and prechronic test data for all chemicals (about 60) from ten contract laboratories on the Toxicology Data Management System (TDMS).

Summary descriptions follow of the NTP's completed, ongoing, and planned activities in toxicology research, testing and test methods development/validation, as well as other key program activities:

Cellular and Genetic Toxicology (See pages 34 to 93)

During FY 1984, tests were completed for gene mutations on 196 chemicals in the *in vitro* microbial assay in *Salmonella typhimurium*, for gene mutations in mammalian cells on 84 chemicals in the L5178Y mouse lymphoma cell assay, for cytogenetic effects on 79 chemicals in an *in vitro* mammalian cell culture system (Chinese hamster ovary cells), and for heritable genetic effects on 37 chemicals in fruit flies (*Drosophila melanogaster*). Testing will continue at comparable levels in FY 1985. Additionally, a comprehensive *in vitro* short-term testing capability is being used both to set priorities for further testing and to develop a data base for a spectrum of genetic toxicities. Between 20 and 30 chemicals were tested in FY 1984 for: (1) gene mutations in bacteria and mammalian cells; (2) chromosome effects in mammalian cells; (3) mammalian cell transformation; and (4) DNA damage/repair.

In test methods development/validation, emphasis is given to *in vivo* mammalian and human somatic cell assay development including: (1) mouse bone marrow cytogenetics; (2) evaluation of the utility of the mouse erythrocyte micronucleus assay; and (3) protocol development and collection of data assessing frequencies of chromosome aberrations and sister-chromatid exchanges in human lymphocytes. Developmental work was completed for *in situ* monitoring of mutagens in the workplace. Validation of assay methodology for measuring germ cell mutations continues as well as cross-test comparisons among the morphological specific locus, biochemical specific locus, and heritable translocation assays.

Carcinogenesis Research and Testing (See pages 94 to 127, 129 to 130, and 154 to 159)

During FY 1984, 13 two-year toxicology and carcinogenesis studies were completed through peer review of the draft technical reports with data audits completed on all prior to review. In FY 1985, the NTP projects completion through the in-life phase of 21 two-year studies, and expects to begin the prechronic phase of toxicity testing for 31 chemicals and the chronic phase for 21 chemicals.

Efforts continue to refine short-term rat liver tumor models for assessing relative initiation/promotion activities of rodent hepatocarcinogens. New initiatives include a study to explore the possible relationship of dietary oil or oil used as a vehicle for gavage studies and pancreatic cancer, and a study to assess the influence of moderate to severe dietary restriction on background tumor rates. Continuing were prechronic and long-term studies of the carcinogenicity of chemicals and substances found in the workplace including silica, foundry molds, roofing asphalt and coal tar pitch condensates.

Toxicologic Characterization (See pages 128 to 137)

Major emphasis remains in use of broadened yet specifically tailored protocols for each chemical in the prechronic testing phase to include a battery of genetic toxicity assays, chemical disposition data, measures of alterations in reproduction and fertility, and other target organ effects as well as clinical and morphological pathology. Studies in biochemical toxicology continue to be concerned with characterizing monooxygenase enzymes which metabolize chemicals, often to toxic products. New initiatives were begun to characterize the toxicity of metals and 1,3-butadiene. As part of the Superfund project, a number of chemicals are being evaluated for several types of toxicity. Microencapsulation is being evaluated as a means of orally administering reactive, volatile, or unpalatable chemicals for toxicology studies.

Chemical Disposition (See pages 142 to 153)

Most chemicals chosen for long-term toxicity testing undergo some degree of chemical disposition evaluation. Special emphasis was given to measuring chemical absorption and toxicity after dermal or oral gavage administration as well as investigating effects of age and body composition on chemical disposition and toxicity. Analytical procedures were developed and applied to monitoring of various metals and solvents, and metabolites in some cases, in the urine or blood of exposed workers.

Chemical Pathology (See pages 154 to 167)

During FY 1984, pathologic findings from 22 interim sacrifice studies were reviewed. Continuing emphasis was placed on improving the quality of histological sections, refining and standardizing tumor nomenclature, and assuring that both tumor and nontumor diagnoses in interim and two-year studies are consistent. New research initiatives include one using NMR imaging for non-invasive detection of tumors or organ damage, and one seeking to characterize spontaneous and chemically-induced tumors for the presence of transforming gene (oncogene) activity.

Cutaneous Toxicology (See pages 168 to 170)

An *in vivo* method for quantitating percutaneous absorption of volatile chemicals was confirmed and applied to studying absorption in animals of benzene, carbon disulfide, ethyl benzene and toluene. Information of this type will be used by chemical managers in optimizing study design for dermal studies.

Immunological Toxicology (See pages 171 to 176)

A number of chemicals of interest to the NTP were screened in the immunotoxicology assay panel for ability to alter immune function and/or host resistance to a challenge. These included cadmium chloride, dimethyl vinyl chloride, pentachlorophenol, nitrobenzene, and benzidine. Research continues on elucidating the mechanisms by which chemical-induced immunotoxicity is mediated.

Neurobehavioral Toxicology (See pages 177 to 181)

The neurobehavioral test battery with continuing refinements is used in the prechronic phase of toxicity testing. Progress was made in construction and in validation of reliability and sensitivity of home cages for monitoring changes in consummatory and motor activity behaviors of animals during exposure to chemicals. Methods for assessing human neurotoxicity from chemicals will be evaluated in the workplace in FY 1985.

Pulmonary Toxicology (See pages 182 to 184)

The study continued comparing pulmonary function tests and radiographic methods with connective tissue analysis and conventional morphologic evaluation as to sensitivity in detecting chemically-induced lesions of the pulmonary system. For Min-U-Sil (crystalline silica), development of fibrotic lesions was more readily disclosed by morphologic evaluation and tissue analysis, while for cadmium there was better correlation among methods. A new primate animal model for evaluating chronic byssinotic effects of chemicals was developed. A two-year inhalation study was completed on the individual and combined effects of coal dust and diesel exhaust regarding pulmonary and mutagenic effects.

Reproductive and Developmental Toxicology (See pages 188 to 198)

In FY 1984, 13 conventional teratology studies on eight chemicals were completed with an additional six studies on four chemicals in progress. Selection of chemicals for conventional teratology testing is being coordinated with selection of chemicals for and results of the short-term *in vivo* reproductive toxicity and sperm morphology/vaginal cytology assays. Data verification has been completed for the five laboratories in the collaborative behavioral teratology initiative, statistical analyses are under way, and a workshop at which data will be presented and future plans discussed is planned for late FY 1985. Members from several chemical classes are being evaluated for effects on fertility and offspring using the fertility assessment by continuous breeding assay. Investigations continued on the reproductive and developmental toxicity of glycol ethers as well as the reproductive toxicity and teratogenicity of a series of industrial alcohols after inhalation exposure.

Resources and Planning Assumptions (See pages 11 to 15)

Using the member agencies' current allocations, the projected NTP budget for FY 1985 provides for a funding level of $76.7 million compared with FY 1984 actual obligations of $77.4 million. There will be continuing emphasis on the development and application of short-term toxicology assays to broaden toxicologic characterization and to aid in designing and/or deciding whether long-term studies are needed.

Oversight and Review (See pages 16 to 21)

The NTP Board of Scientific Counselors held one meeting at the NCTR where it received an orientation to the Center's NTP-related programs. At a second meeting, the Board reviewed programs in biochemical toxicology, chemical disposition and immunotoxicology. The *Ad Hoc* Panel on Chemical Carcinogenesis Testing and Evaluation presented its final report to the Board, in general, endorsing the directions taken by NTP's carcinogenesis studies programs. The Technical Reports Review Subcommittee of the Board reviewed and approved in public session the technical reports for 13 two-year toxicology and carcinogenesis studies.

Data Management and Analysis (See pages 244 to 250)

The Toxicology Data Management System (TDMS), developed to collect, store and process data for NTP chronic and prechronic studies, is now collecting in-life chronic and prechronic test data for all chemicals on test in ten NTP contract laboratories. There are data for about 60 chemicals on the TDMS data base.

Chemical Nomination and Selection (See pages 201 to 223)

During FY 1984, 58 chemicals were nominated to the NTP for extensive toxicological testing. Additionally, a larger number were nominated for genetic toxicology or special effects testing. The Executive Committee selected 14 chemicals as FY 1984 priority chemicals for in-depth toxicologic evaluation.

INTRODUCTION

Background

The earliest Federally mandated attempts to address chemical toxicity took place in the pharmaceutical and food additive industries, where extensive safety testing was required by the Federal Food, Drug, and Cosmetic Act. This testing, however, was primarily for acute effects and did not address the consequences of long-term exposure to chemical agents. In the early 1960s the National Cancer Institute (NCI) began a program to determine whether particular substances could cause cancer in experimental animals as a result of long-term, low-level exposure, as well as a screening study of pesticides to determine if they were carcinogenic. These early efforts were the antecedent of the NCI's carcinogenesis bioassay program. This laboratory testing contributed greatly to the knowledge regarding the carcinogenic potential of chemicals, but did not attempt to predict for toxic effects other than cancer.

Paralleling these program efforts, other research advances were being made that eventually would permit a more comprehensive approach to the problems of chemical toxicity. Information was developed that indicated mutagenic compounds also may be carcinogenic -- which in turn held some promise for decreasing the number of compounds that require testing in a complete cancer bioassay. These findings resulted in great energy and resources being invested in developing rapid and inexpensive means to establish the potential toxicity of chemical substances.

Throughout this period, there was major legislative activity to provide legislative tools to reduce or prevent exposure to hazardous substances. This new legislation (including the Toxic Substances Control Act or TSCA) greatly increased the regulatory agencies' needs to know more about the toxicity of environmental agents.

By the latter part of the 1970s, the various Federal agencies had begun to develop or intensify test programs in a variety of areas, in response to each of their mandates on research needs. Most of these test programs were limited in scope, and therefore did not take into account either exposure sources or toxicities other than the ones of specific interest to the sponsoring agency. In addition, the research and regulatory agencies often were examining the same compounds, but for different reasons, thereby contributing to a sense of overlap and duplication. Thus, it became apparent that the Nation's toxicology testing capacity was not being used to best advantage, and could benefit from better coordination and program integration. It was against this backdrop of scientific, regulatory, and congressional concerns that the National Toxicology Program (NTP) was established on November 15, 1978.

Accomplishments

The NTP attempts to focus relevant Public Health Service programs on four overarching objectives:

- Broadening the spectrum of toxicologic information which is obtained on chemicals selected;
- Increasing the numbers of chemicals tested, within funding limits;

- Developing and validating a series of tests and protocols more appropriate for regulatory needs; and

- Communicating plans and results to governmental agencies, the medical and scientific communities, and the public.

NTP began with the resources brought to it by its member agencies -- resources for which there were often already long-range obligations that had to be met. Thus, it was only into approximately its third year of operation that real changes in program direction and balance became apparent. Over its nearly six-year existence, in toxicity testing alone, the NTP's capabilities have evolved from a limited collection of routine individual testing activities primarily -- (1) a standard two-year carcinogenesis bioassay; (2) a prechronic toxicology screen providing limited information on specific types of toxicity; (3) a conventional teratology assay; and (4) the Salmonella/microsome mutagenesis test -- to an integrated program of testing of chemicals for multiple endpoints using specifically tailored assay protocols. During this time, the development, validation, and application of better, more specific, more rapid and less expensive test methodologies have evolved as the core of NTP scientific activity.

Thus, the NTP has expanded the traditional two-year carcinogenesis test into a comprehensive toxicology study which provides definitive information not only on a chemical's potential to cause cancer in experimental animals, but also on its other effects including genetic toxicity, chemical disposition, major organ toxicity, and effects on fertility and reproduction. The genetic toxicity assays include measurements of gene mutations in bacterial and mammalian cells, chromosome damage, mammalian cell transformation, major organ toxicity, and effects on fertility and reproduction. The genetic toxicty assays include measurements of gene mutations in bacterial and mammalian cells, chromosome damage, mammalian cell transformation, and DNA damage/repair. Other endpoints which are monitored where indicated include tests for neurobehavioral and immunologic toxicity, and endocrine effects. This expanded testing should lead to better dose-effect extrapolation from labaratory animals to humans and is central to the Public Health Service's role in disease prevention.

Developmental activities include investigation of short-term in vivo assays to detect chemicals which may cause liver, urinary bladder, and skin cancers. NTP is also seeking to increase insight into how chemicals cause various effects; for instance, in vitro systems are being studied that should provide knowledge into the mechanisms of genetic toxicity and carcinogenesis. Finally, NTP is seeking to develop alternatives to whole animal testing.

Through development of several new means for disseminating information, the NTP has managed to open the science decision-making process so that interested and affected parties can take part. This, in turn, leads to improvements in the NTP program, through increasing its responsiveness, decreasing duplicative efforts, and enabling it to make better-informed decisions.

Program activities supporting the primary NTP objectives are discussed in the following chapters. These cover program resources, oversight and review, coordination and communication, organizational structure, ongoing and planned efforts in toxicology research, testing, and test methods development and validation, chemical nomination and selection, information generation and dissemination, and data management and analysis. Information on current FY 1984 efforts is separated from planned activities for FY 1985 and beyond, and current programs and projects are associated with a contact person. Accomplishments and plans are also described separately by agency under each scientific and management section.

RESOURCES AND PLANNING ASSUMPTIONS

The National Toxicology Program (NTP) consists of the relevant toxicology activities of the National Institutes of Health's National Institute of Environmental Health Sciences (NIH/NIEHS); the Food and Drug Administration's National Center for Toxicological Research (FDA/NCTR); and the Centers for Disease Control's National Institute for Occupational Safety and Health (CDC/NIOSH).* The National Institutes of Health's National Cancer Institute (NIH/NCI), a charter agency, remains active in the Program through membership on the NTP Executive Committee.

The NTP relies on voluntary allocations from its three member DHHS agencies, the amounts of which are specified in memoranda of understanding after yearly appropriations are known. Obligations in FY 1984 were $77.4 million. Using the member agencies' current allocations, the budget for FY 1985 would provide for a funding level of $77.0 million. (The estimated budget for FY 1985 is compared with the actual obligations for the past six fiscal years in Figure 1.)

As in past years, most resources are spent on testing chemicals for carcinogenic, mutagenic, teratogenic, and other target organ toxic effects (Figure 2). Two-year toxicology and carcinogenesis studies account for a large proportion of these resources.

The NTP has stabilized at 20 to 25 the number of chemicals started in prechronic testing each year and has expanded the information developed in this phase to provide a better basis for deciding whether chronic testing is warranted. During this phase, studies of reproductive function, a comprehensive battery of short-term assays measuring cellular and genetic toxicity, measures of chemical disposition, as well as one or more special studies are incorporated into experimental design protocols. Additionally, testing of all chemicals nominated specifically for genetic toxicologic evaluation continues in Salmonella and, where indicated, in Drosophila, Chinese hamster ovary cells, and the L5178Y mouse lymphoma mutation system. For those chemicals proceeding to chronic testing, most studies include three dose levels plus controls in both sexes of two rodent species, as well as a 15-month interim sacrifice to provide more information on chronic toxicity.

Finally, NTP will continue conventional teratology testing on 10 to 15 chemicals in FY 1985. Selection of chemicals chosen for testing will be aided by the results of a short-term in vivo reproductive toxicology assay, as well as sperm morphology and vaginal cytology assays now routinely incorporated in 90-day prechronic studies.

As noted above, the use of short-term toxicology tests provides data aiding in decisions whether to conduct long-term studies. Over time, more extensive use of existing short-term tests coupled with development, validation and application of better, more specific, and more sensitive test systems will reduce the number of chemicals requiring chronic testing. This in turn will allow more emphasis on short-term test development and even broader and more in-depth information on the chemicals committed to long term tests. (Figure 3 shows the division of funding levels in FY 1984 among testing, methods development, and test validation for the major program areas of mutagenesis, fertility and reproduction, toxicological characterization and carcinogenesis.) Whatever the program balance over time, however, the combination of these composite data will aid health regulatory agencies and the biomedical community in assessment and estimation of human health hazards from chemicals and will help them take steps to preventing these hazards.

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*Other Federal agencies also conduct significant toxicology activities. Current information on many of these efforts may be found in the companion volume to the Annual Plan, the FY 1985 Review of Current DHHS, DOE, and EPA Research Related to Toxicology.

FIGURE 1

AGENCY ORIGIN AND AMOUNTS OF FUNDING (millions)
NATIONAL TOXICOLOGY PROGRAM

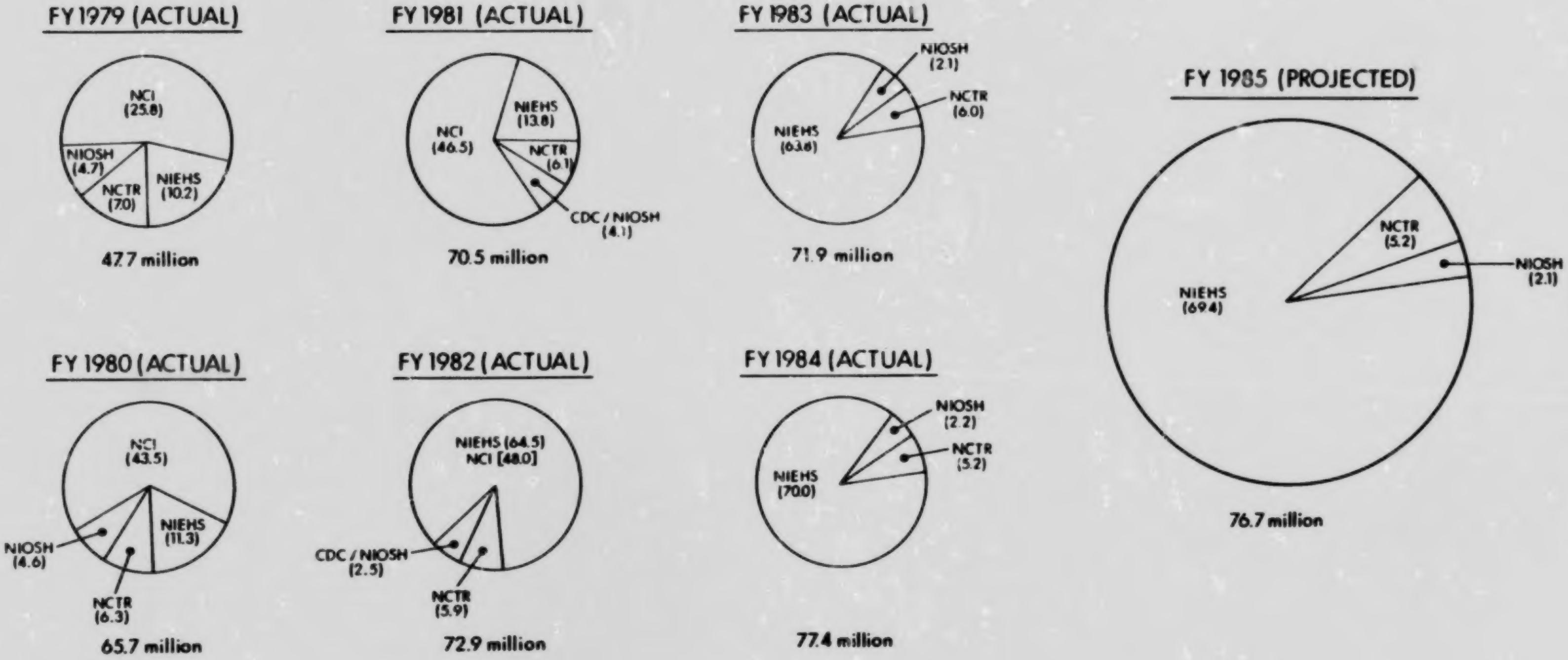
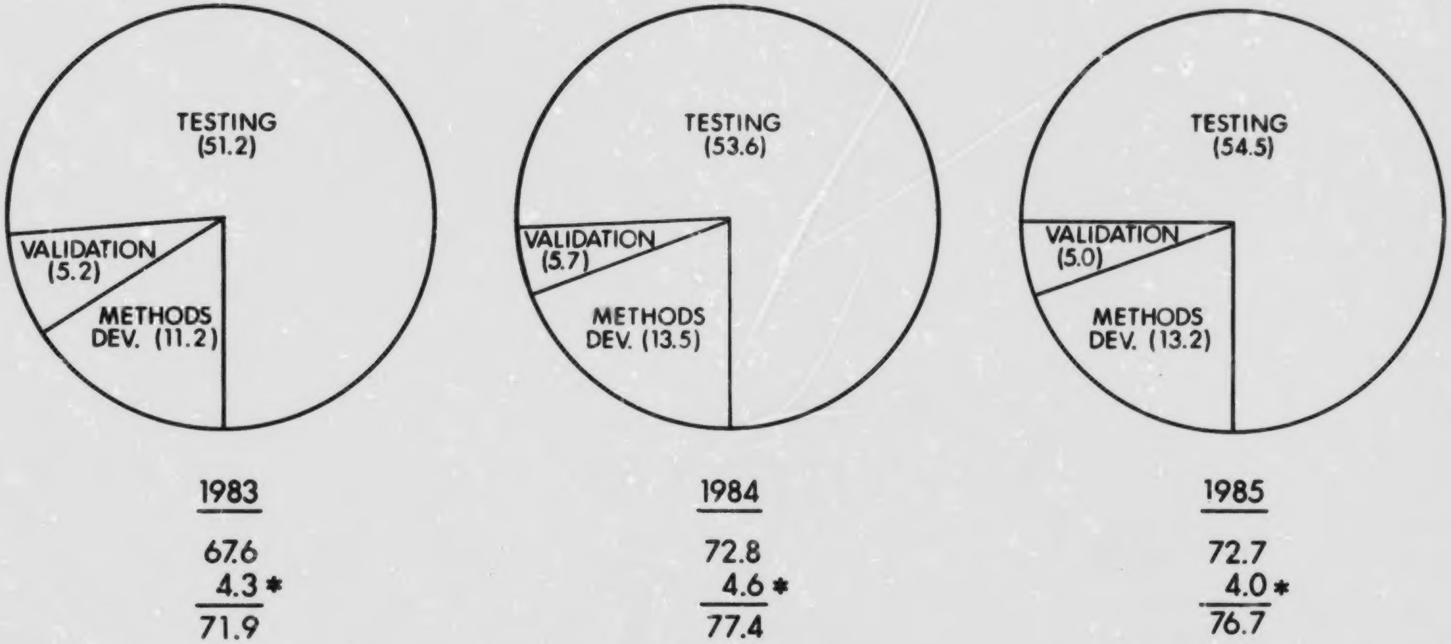


FIGURE 2

FUNDING LEVELS BY PROGRAM ACTIVITIES- FY 1983 - 1985
NATIONAL TOXICOLOGY PROGRAM (millions)



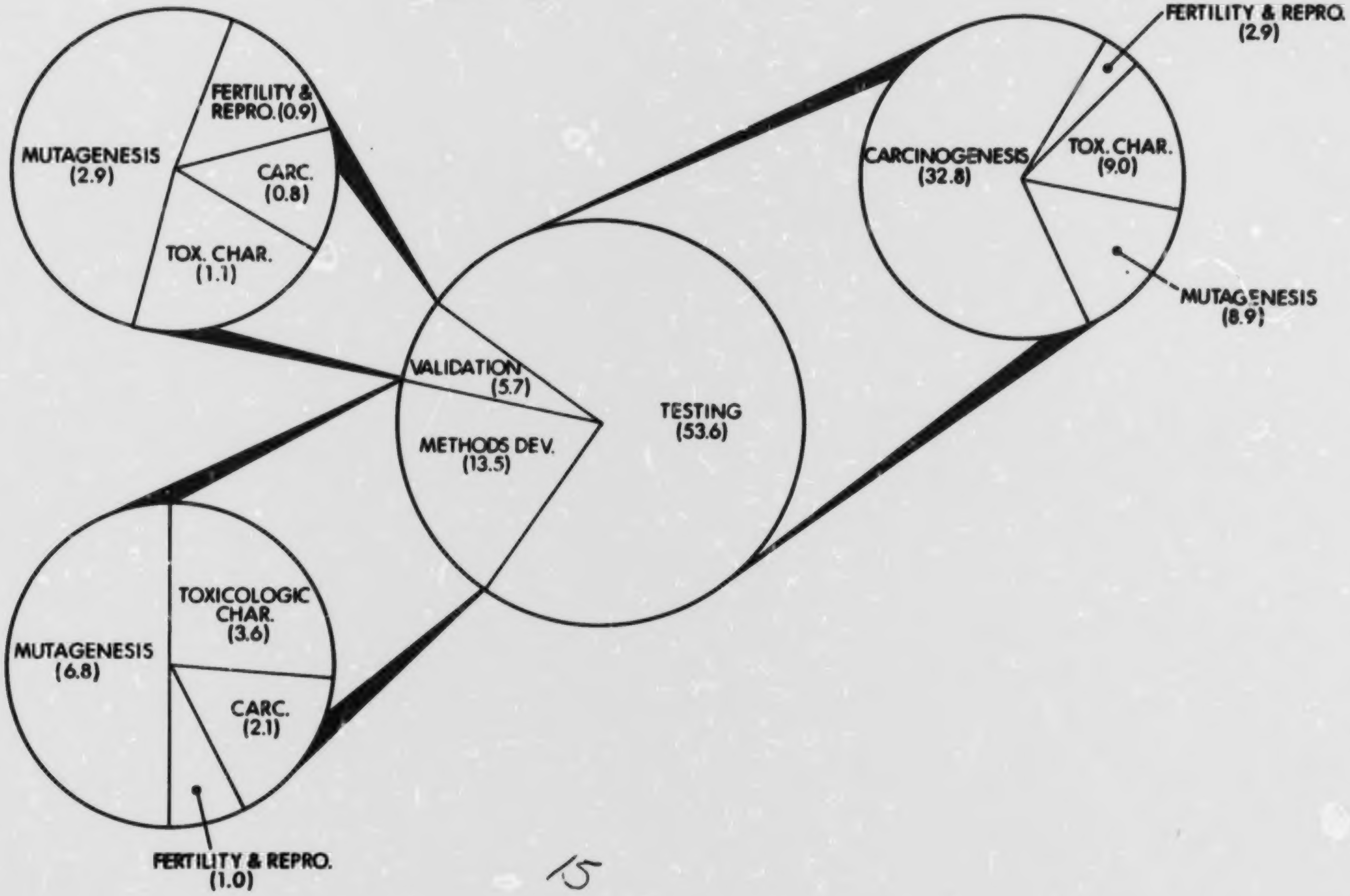
* Includes other activities such as veterinary pathology training grants, WHO Cooperative Center, indirect operational support, etc.

Note : Excludes all Superfund activities

FIGURE 3

FUNDING LEVELS BY PROGRAM ACTIVITIES BY PROGRAM AREA - FY 1984

NATIONAL TOXICOLOGY PROGRAM (millions)
1984



OVERSIGHT AND REVIEW

NTP activities are coordinated under the leadership of the Program Director, Dr. David Rall, who for purposes of the NTP reports to the Assistant Secretary for Health, DHHS. However, since the NTP's scientific tasks are so complex and involve integrating several agencies' activities, it is necessary for more than a single body to oversee and review the Program.

PRIMARY OVERSIGHT

- Executive Committee

Primary program oversight is provided by the NTP Executive Committee. Composed of the heads of health research and regulatory agencies, it serves as NTP's major advisory group on research and testing needs, on selection and priority-setting for the specific chemicals to be tested, and as a forum for discussion of science policy issues and information exchange among agency heads. The Executive Committee also reviews and approves the NTP Annual Plan. Thus, through the Executive Committee, the NTP assures continuing communication between member health research and health regulatory agencies and receives advice about critical phases of its operation, including program planning and balance.

Members of the Executive Committee at the end of FY 1984 were:

Dr. Edward N. Brandt, Jr., Assistant Secretary for Health, Department of Health and Human Services (non-voting);

Dr. Vincent T. DeVita, Jr., Director, National Cancer Institute;

Dr. J. Donald Millar, Director, National Institute for Occupational Safety and Health;

Dr. David P. Rall, Director, National Institute of Environmental Health Sciences;

Mr. Robert A. Rowland, Assistant Secretary of Labor for Occupational Safety and Health Administration, Department of Labor;

Mr. William Ruckelshaus, Administrator, Environmental Protection Agency (Chairperson);

Mrs. Nancy Steorts, Chairman, Consumer Product Safety Commission;

Dr. James B. Wyngaarden, Director, National Institutes of Health; and

Dr. Frank E. Young, Commissioner, Food and Drug Administration.

The Chairperson is elected by the Committee and serves a one-year term. The Committee itself meets three to four times yearly.

SCIENTIFIC OVERSIGHT AND REVIEW

- Peer Review Process

Peer Review of NTP projects is a multi-level process involving review of project concepts, project proposals, and completed technical reports. Within the NIEHS, the Toxicology Research and Testing Program Management Committee (see Organization section) performs an initial review of the NIEHS/NTP research and testing proposals. The Board of Scientific Counselors (discussed further below) is the principal body providing scientific oversight and review. The Board performs external peer review of concepts for all NIEHS/NTP and relevant NIOSH contract, cooperative agreement, and interagency agreement proposals to advise on their relevance, need, and priority.*

Once grant applications or contract proposals for projects are submitted to the NIEHS/NTP, they are evaluated for scientific merit by the Environmental Health Sciences Review Committee (EHSRC). The EHSRC, which was established as part of the NIH-wide peer review process, is composed of 21 members with expertise in pharmacology, toxicology, pathology, biochemistry, mutagenesis, and clinical disciplines.

When projects are completed and draft technical reports on the results are prepared, the Technical Reports Review Subcommittee of the Board of Scientific Counselors, supplemented by an ad hoc panel of expert reviewers, evaluates the reports for technical and scientific merit.

- Board of Scientific Counselors

The Board, which is composed of eight non-governmental scientists appointed by the Assistant Secretary for Health, DHHS, reviews the Program for scientific adequacy and helps identify program needs, assisted on particular issues by scientists with relevant specialties.

Current members of the Board are:

Norman E. Breslow, Ph.D., Professor of Biostatistics, Department of Biostatistics, University of Washington;

Leila Diamond, Ph.D., Professor, Wistar Institute;

Curtis Harper, Ph.D., Associate Professor of Pharmacology, University of North Carolina School of Medicine;

Jerry B. Hook, Ph.D., Vice President, Preclinical Research and Development, Smith Kline and French Laboratories;

Jeanne M. Manson, Ph.D., Associate Director, Developmental Toxicology, Smith Kline and French Laboratories;

Mortimer L. Mendelsohn, M.D., Ph.D., Associate Director, Biomedical and Environmental Research Program, Lawrence Livermore Laboratory, University of California (Chairperson);

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*A similar peer review mechanism is applied to all NIOSH-funded NTP proposals

Henry C. Pitot, M.D., Ph.D., Professor of Oncology and Pathology, and Director, McArdle Laboratory for Cancer Research, School of Medicine, University of Wisconsin;

James A. Swenberg, D.V.M., Ph.D., Chief, Pathology Department, Chemical Industry Institute of Toxicology.

The Board generally meets three times a year in public sessions. The two meetings held in FY 1984 are summarized as follows:

March 27-28, 1984, Meeting, Jefferson, Arkansas (NCTR)

The Board received an extensive orientation to NCTR and selected NCTR science programs, many of which related directly to NTP. Included were: programs in developmental and reproductive toxicology; biochemical toxicology; microbiology; mutagenesis and molecular toxicology; biometry; and a progress report on the Toxicology Data Management System, a computer system developed at NCTR which is being used to collect data from NTP prechronic and chronic studies.

The Board also reviewed and approved NIOSH/NTP concept proposals for interagency agreements dealing with inhalation development and reproductive toxicology, and evaluation of Drosophila for teratogen screening. Three NIEHS/NTP concept proposals to be done on contracts were reviewed and approved: (1) testing the urine of rats on prechronic tests for mutagenic activity; (2) examination of immunotoxicity by chemical xenobiotics; and (3) provision of data auditing support resources. Finally, the Board approved formation of an advisory review panel in support of the NTP Reproductive and Developmental Toxicology Program.*

August 16-17, 1984, Meeting, Research Triangle Park, North Carolina (NIEHS)

The Board and ad hoc expert consultants conducted peer review of NIEHS/NTP Systemic Toxicology Branch programs in biochemical toxicology, chemical disposition and immunotoxicology. It also approved NIEHS/NTP concept proposals for contract studies addressing the effect of the Ah locus on lifespan and pathology of congenic mice, and development of ovarian toxicity screening methods (studies on the classification of ovarian follicles as an indication of ovarian toxicity). The Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation (discussed further below) also presented its final report to the Board. The Board reviewed 27 chemicals (including six chemicals deferred from a previous meeting) which had been nominated for testing and previously evaluated by the NTP Chemical Evaluation Committee. The Board's recommendations and priority rankings were incorporated into the final literature summaries sent to the NTP Executive Committee.

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*The review panel was formed and met once in FY 1984 to review the various projects which comprise the Program.

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Summary minutes of the two Board meetings held in FY 1984 are available on request. (CONTACT PERSON: Dr. L. G. Hart, NIEHS)

Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation -- The Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation was established in response to a recommendation from the March 1983 meeting of the National Toxicology Program (NTP) Board of Scientific Counselors. The charge to the Panel was to review the basic biology and chemistry of carcinogenesis and to recommend to the Board of Scientific Counselors methods that NTP should use for the detection and evaluation of chemical carcinogens. The Panel was expected to survey the state-of-the-art reflecting advances made since the last thorough published evaluation of chemical carcinogenesis testing by the NCI in the 1970s. During the fall and winter of 1983, three Panel subgroups prepared draft reports for their areas: short-term tests; data required from prechonic studies; and design of chronic studies. A working session was held on January 13, 1984, in Washington, D.C., to review progress of the draft reports, remove duplication, and prepare a preliminary integrated Panel report. Availability of this report was announced in the Federal Register in February with approximately five weeks allowed for public comments. The Panel met again on May 3 and 4, 1984, in Research Triangle Park, North Carolina, to revise the report as appropriate, based on the large volume of comments received. A final report was then prepared and formally presented to the Board of Scientific Counselors on August 17, 1984.

In the report, the conclusions of the Panel are stated as a series of recommendations to the Board, dealing with practical aspects of short-term, prechronic and chronic studies as well as possible future studies extending methodology and resolving persistent questions. The Panel found that the NTP's ongoing effort has benefited from the existing peer review process and was continuing to evolve scientifically, that the issue of quality assurance was gaining appropriate recognition, and that many of the Panel's recommendations were in fact anticipated and being implemented by the NTP. The NTP will formally respond to the recommendations of the Panel report at a public meeting of the Board in FY 1985.

Copies of the Report of the NTP ad hoc panel on Chemical Carcinogenesis Testing and Evaluation are available without charge from: NTP Public Information Office, MD B2-04, Box 12233, Research Triangle Park, N.C. 27709. Telephone: (919) 541-3991, FTS: 629-3991.

- Technical Reports Review Subcommittee

During FY 1984, the Subcommittee and Ad Hoc Panel of experts met in open session in October, March, and July. Peer review was completed on the technical reports for 13 toxicology and carcinogenesis studies. (See Table 9 in the Carcinogenesis Research and Testing section.)

Additionally, the Subcommittee and panel met twice to conduct special reviews at the request of the Center for Food Safety and Applied Nutrition, Food and Drug Administration (FDA). They met on October 27, 1983 in Research Triangle Park to review the data from the chronic carcinogenesis bioassay of FD and C Red No. 3, and again on July 26, 1984, in Research Triangle Park to review the data from the chronic carcinogenesis bioassay of D and C Red No. 33.

These bioassays were submitted to the FDA to support permanent listing of the dyes. The Subcommittee was augmented by an expert consultant in pathology for each review.

Summary minutes of the three regular and two special review meetings of the Subcommittee and panel held in FY 1984 are available on request. (CONTACT PERSON: Dr. L. G. Hart, NIEHS)

The members of the Subcommittee and panel of experts during FY 1984 were as follows:

Subcommittee

- Dr. Jerry B. Hook (Chairperson)
- Dr. Curtis Harper
- Dr. James Swenberg

Ad Hoc Panel

- Dr. Louis S. Beliczky, Department of Industrial Hygiene, United Rubberworkers International Union;
- Dr. Devra L. Davis, Board on Toxicology and Environmental Health Hazards, National Academy of Sciences;
- Dr. Robert M. Elashoff, Jonsson Comprehensive Cancer Center, University of California at Los Angeles (Ended October 1983);
- Dr. Seymour L. Friess, Consultant in Toxicology;
- Dr. J. Michael Holland, Department of Pathology, Chevron Environmental Health Center (Ended October 1983);
- Dr. Thomas C. Jones, New England Regional Primate Research Center, Harvard Medical School (Began March 1984);
- Dr. Richard J. Kociba, Dow Chemical USA (Began March 1984);
- Dr. David Kotelchuck, United Electrical, Radio and Machine Workers of America (Began March 1984);
- Dr. Robert A. Scala, Exxon Corporation (Ended October 1983);
- Dr. Thomas Slaga, University of Texas System Cancer Center;
- Dr. Steven R. Tannenbaum, Department of Nutrition and Food Science, Massachusetts Institute of Technology (Began March 1984);
- Dr. Bruce W. Turnbull, College of Engineering, Cornell Unviersity (Began March 1984);
- Dr. John R. Van Ryzin, Division of Biostatistics, School of Public Health, Columbia University;

- Dr. Stan D. Vesselinovitch, Department of Radiology and Pathology, University of Chicago (Ended October 1983);
- Dr. Mary Vore, Pharmacology Department, University of Kentucky, College of Medicine (Ended October 1983).

COORDINATION AND COMMUNICATION

Both the communication of NTP's activities, research findings, testing results and new test methods as well as coordination of related scientific programs among agencies are key to NTP's success. Communication is pursued in a variety of ways:

COMMUNICATIONS

Reports -- The development and approval of the Annual Plan by the DHHS member agencies (NIEHS, NCTR, and NIOSH) is central to the communication and coordination process. The Plan is the principal description of the toxicology research, test development, and chemical testing efforts coordinated among the relevant health research and regulatory agencies; it represents NTP's current strategy for testing, test methods development and validation, and it details the NTP's accomplishments in the preceding fiscal year. Part II of the Annual Plan, the Review of Current DHHS, EPA, and DOE Research Related to Toxicology, describes toxicology underway in other agencies. Finally, the NTP Technical Bulletin, published periodically, serves as a more frequent communication of NTP's recent, current, and upcoming activities, including abbreviated experimental results.

Open Meetings and Exhibits -- These media are important in providing the public an opportunity to comment on and receive information about the Program. For instance, an NTP scientific exhibit was presented at annual meetings of the Teratology Society, June 24-29, 1984, and the Industrial Union Department, AFL-CIO, October 3-4, 1984.

INTERAGENCY COORDINATION

The NTP also promotes information exchange and scientific collaboration among those addressing common problems of chemical toxicology. The common membership on the Executive Committee of the health research and health regulatory agencies is in itself an important means of fostering this exchange. These agencies review and comment on all of the NTP Annual Plans, make presentations to the Executive Committee on their activities which are of interest both to the NTP and other member agencies, and participate in NTP-sponsored meetings and briefings on scientific and public issues.

The regulatory agencies are also an important source of nominations to the NTP for various types of toxicological testing, and have participated in reviewing, evaluating, and ranking of substances nominated for testing. At the Executive Committee level they have cast votes to select, defer, or reject evaluated chemicals. NTP personnel regularly consult staff from given regulatory agencies in the preparation of test protocols for selected chemicals nominated for testing by those agencies, so that the results emanating from such tests will be useful for regulatory endpoints; coordination is also encouraged throughout the conduct of the tests and the analysis of results. In addition, the regulatory agencies have contributed data to the three Annual Reports on Carcinogens published thus far.

The regulatory agencies particpating in the NTP have utilized toxicology test data generated by the NTP on various environmental chemicals in their analyses of the need for regulation of these chemicals. For example, the positive results from the NTP carcinogenesis study of 1,3-butadiene in mice were utilized by EPA in deciding to initiate a 180-day review of the chemical under

Section 4(f) of the Toxic Substances Control Act. Similarly, OSHA has published a notice in the Federal Register requesting interested parties to submit data and comments relevant to determining the risk of potential adverse health effects of 1,3-butadiene. In addition, a number of recent proposed regulatory actions have been based in part on data from NTP toxicology studies. As an example, EPA made use of the positive results from the two NTP/NCI carcinogenesis bioassays of ethylene dibromide in its decision to eliminate certain uses of this chemical as a pesticide.

The regulatory agencies have also requested that the NTP undertake additional toxicology testing of chemicals demonstrated to have adverse effects in completed NTP studies in order to better elucidate their mechanisms of action.

For example, the agencies have requested further studies of 1,3-butadiene to develop dose response carcinogenicity data in mice and to investigate the species differences in sensitivity to the carcinogenic affects of the chemical in rodents. In addition, the agencies supported genotoxicity and reproductive effects testing of the chemical. Based on preliminary results made available to agency representatives from the ongoing NTP carcinogenicity study of methyl carbamate, these persons requested genotoxicity, reproductive effects and pharmacokinetic testing of the chemical.

Two efforts under way since FY 1981 also illustrate the NTP role in interagency coordination:

The Benzidine Dye Initiative, developed to study the toxicology and carcinogenicity of a class of dyes derived from benzidine, 3,3'-dimethylbenzidine, and 3,3'-dimethoxybenzidine, continues as a collaborative research initiative among NIEHS, NCTR, and NIOSH. Activities in two main areas of research and testing, chemical disposition and metabolism, and genetic toxicology, were completed in FY 1984, and activities in in vivo toxicology and carcinogenicity testing will continue in FY 1985. The FY 1984 accomplishments as well as future plans are described in the section on the Benzidine Dye Initiative. (CONTACT PERSON: Dr. J. Mennear, NIEHS)

The NTP/EPA Clearinghouse on Phthalates was created in response to unanimous recommendation of the Federal health regulatory and research agencies made at the June 1981 Conference on Phthalates. Persons or organizations planning, conducting, or having completed research on the toxicological effects of these compounds are requested to contact Ms. Florence Jordan, NTP/EPA Clearinghouse on Phthalates, Room 1813, Building 18, North Campus, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, North Carolina 27514 Telephone: (919)-541-3418 FTS: 629-3418.

Research studies on phthalic acid esters by the NIEHS are described in detail in the section on Ortho Phthalic Acid Esters - Safety Evaluation. In addition, Dr. W. Kluwe, NIEHS/NTP, was a member of the program subcommittee and presented two papers at the International Conference on Phthalic Acid Esters held at the University of Surrey, Guildford, England, on August 6-7, 1984.

Toxicology Data Management System (TDMS) -- A new interagency agreement between NIEHS and NCTR that can be extended up to three years was initiated to continue implementation of this data management system for collection, storage, and retrieval of carcinogenicity and toxicology data. Reports of FY 1984 accomplishments can be found in the Data Management and Analysis section.

Superfund Activities -- In continuing support of the Public Health Service responsibilities under the Comprehensive Environmental Response, Compensation and Liability Act (commonly called Superfund), NTP conducts toxicology testing on chemicals for which adequate data are not available, and which have been identified in priority hazardous waste sites or as released otherwise into the environment.

As chemicals are identified by the Environmental Protection Agency (EPA), they are referred to an interagency Subcommittee of the DHHS Committee to Coordinate Environmental and Related Programs to determine whether there is sufficient toxicological information on a chemical. If not, the Subcommittee nominates it for NTP testing, and NTP in turn determines the appropriate tests to be undertaken. The results of testing are disseminated broadly in accordance with general NTP procedures. Ongoing and planned testing activities are described in detail in the Superfund Project subsection of the section on Toxicologic Characterization. (CONTACT PERSONS: Dr. W. Kluwe and Dr. R. Yang, NIEHS)

Other Activities -- NTP staff continue to participate in interagency liaison groups, including the DHHS Committee to Coordinate Environmental and Related Programs, the Task Force on Environmental Cancer and Heart and Lung Disease, and the Interagency Collaborative Group on Carcinogenesis.

Additionally, a memorandum of understanding between the NTP and the U.S. Army Medical Research and Development Command (USARMRDC) was renewed until 1986. The agreement serves as authority for specific agreements for conducting joint projects, exchanging compounds for identification and testing, and cross validation of research methodologies.

INTERNATIONAL COORDINATION

NTP maintains its varied liaison with foreign agency counterparts. Included are the World Health Organization (WHO) and the WHO's International Program on Chemical Safety (IPCS), the International Agency for Research on Cancer (IARC), the United Nations Environment Program's (UNEP's) International Registry of Potentially Toxic Chemicals (IRPTC), the International Commission for Protection Against Environmental Mutagens and Carcinogens (ICPEMC), the European Chemical Industry Ecology and Toxicology Center (ECETOX), and various governments and individual scientists throughout the world. For instance, an agreement is maintained with the IARC for a registry of persons exposed to phenoxy herbicides and contaminants, particularly the chlorinated dibenzofurans. (CONTACT PERSON: Dr. J. Huff, NIEHS)

ORGANIZATION

As noted previously, the NTP is composed of relevant programs of the National Institutes of Health (NIH), the Centers for Disease Control (CDC), and the Food and Drug Administration (FDA). The NIH component, the National Institute of Environmental Health Sciences (NIEHS), represents the majority of the NTP budget, and is administered by the Director and NTP staff at NIEHS. The CDC's component, the National Institute for Occupational Safety and Health (NIOSH), and the FDA's component, the National Center for Toxicological Research (NCTR), are not under direct NTP management but each participates fully in overall NTP activities.

The NTP Steering Committee, formed in 1980, promotes NTP working relationships. Composed of the NTP Director, the operating heads of the three contributing agencies, and key support staff, the Committee meets three to four times yearly. The Committee reviews ongoing and proposed programs and projects, resolves interagency problems, makes agency allocations for chemicals approved for testing by the Executive Committee, and plans agendas for upcoming NTP meetings. Within each agency are staff who act as coordinators or program leaders in the major NTP scientific and program support segments.

The program segments of the NTP can be grouped broadly into two categories --toxicologic research and testing, and coordinative management activities. These activities are described briefly by agency as follows:

NIEHS -- The Toxicology Research and Testing Program (TRTP) comprises the NIEHS testing, test development, and management activities. The TRTP is responsible for all NIEHS/NTP operations and is composed of six branches:

- Carcinogenesis and Toxicology Evaluation Branch
  - Designs and interprets toxicologic, carcinogenicity and related studies on chemicals.
  - Develops data that elucidate general and specific mechanisms involved in toxic responses to chemicals.
  - Provides logistical support for coordinating and scheduling the contract testing functions. Oversees contract awards and conduct of studies at contract laboratories.
- Cellular and Genetic Toxicology Branch
  - Develops and validates in vivo and in vitro methods to detect and define effects of chemicals on genetic components.
  - Investigates genetic damage in somatic as well as germ cells.
  - Studies effects of chemicals on experimental organisms and to a far lesser extent on human populations.
- Chemical Pathology Branch
  - Provides pathology support to all segments of the Program, especially critical to long-term toxicology and carcinogenesis studies.

  - Develops standards for tumor and non-tumor pathology diagnoses and nomenclature.
  - Develops clinical chemistry parameters for assessing cellular and organ function.
- Program Resources Branch
  - Serves as a resource for chemical acquisition and storage, laboratory animal breeding and allocation, and general laboratory health and safety.
- Systemic Toxicology Branch
  - Studies target organ toxicities and develops methods for assessing toxic effects involving immune, pulmonary, reproductive, and renal functions.
  - Performs studies to expand basic knowledge of chemical absorption, distribution, metabolism, and excretion.

The five branch chiefs and several other key staff persons form the TRTP Management Committee. The Committee, chaired by the Director, TRTP, meets twice monthly, and is responsible for planning, review and implementation of NIEHS/NTP activities.

Finally, the Program Resources and Carcinogenesis and Toxicology Evaluation Branches, along with information generation and dissemination activities (managed from the Office of the Director, TRTP), and data management and analysis functions (provided by the Data Management and Analysis group of the NIEHS Biometry and Risk Assessment Program), constitute a major segment of coordinative management activities supporting the research and testing efforts and provide information on program plans and progress. Additionally, the Office of the Director, TRTP, is responsible for monitoring quality assurance and good laboratory practices at the testing laboratories.

NIOSH -- The NTP program of NIOSH consists of research projects and related activities from three Divisions: the Division of Biomedical and Behavioral Science, the Division of Respiratory Disease Studies, and the Division of Standards Development and Technology Transfer. The contributions to the NTP from these three divisions are outlined below.

- Division of Biomedical and Behavioral Science, located in Cincinnati, Ohio,

  This Division conducts the bulk of NIOSH's research in toxicology. The NTP projects from this group fall into the areas of general toxicology, carcinogenicity, reproductive toxicology, neurotoxicology, and cutaneous toxicology. Toxicologic studies in this division emphasize inhalation exposures.

- Division of Respiratory Disease Studies

  This division conducts research on the mutagenicity of materials found at the workplace. Methods are developed or refined to detect mutagens of occupational significance. The division is located in Morgantown, West Virginia.

- Division of Standards Development and Technology Transfer

  The Cincinnati-based division provides toxicology information to the NTP in the form of evaluations of published literature on chemical hazards, recommendations for chemicals proposed to evaluations, and other services as requested.

Several scientists from NIOSH serve as chemical managers for chemicals being tested by NTP. Senior scientists from NIOSH are members of the NTP committees concerned with chemical nominations, data auditing, and discipline-specific activities.

NCTR -- The National Center for Toxicological Research (NCTR) supports the NTP in a number of areas. Most of NCTR's contributions are provided by the following divisions:

- Division of Teratogenesis Research

  Staff members serve as project officers and coordinators for NTP teratology, behavioral and developmental teratology, and reproductive toxicology studies.

- Division of Mutagenesis Research

  This division conducts studies for NTP in the area of cellular and genetic toxicology, develops and validates in vitro and in vivo systems for determining genotoxicity of chemicals, and tests NTP compounds in the primary hepatocyte/DNA repair system and the heritable translocation assay.

- Division of Carcinogenesis Research

  Division staff perform chemical disposition and metabolism studies, study the activation and inactivation of toxic compounds and the mechanism of action of carcinogens, and conduct prechronic and chronic studies on NTP chemicals.

- Division of Chemical Toxicology

  This division conducts prechronic and chronic studies on NTP chemicals, as well as research involving toxicity and carcinogenicity of chemicals in whole animal experiments, and the chemical disposition of selected compounds.

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- Division of Toxicology Data Management Systems

  This division leads in the development and utilization of computer based systems for data collection, storage, and evaluation for NTP chronic bioassays. This division also coordinates the acquisition and utilization of hardware by various contractors and the development of software for various NTP programs.

Finally, all three member agencies are particularly involved in chemical nomination and selection, and chemical and laboratory test management. Chemical nomination involves the evaluation and priority ranking of chemicals by staff from all the agencies on the Executive Committee. Staff members at each agency are assigned as chemical managers for individual compounds to serve as a focus for the scientific aspects of the studies on that chemical. Laboratory management is carried out by scientists serving as project officers, to ensure that each toxicological study is conducted in a proper and timely fashion (see Chemical and Laboratory Test Management Section).

TOXICOLOGY RESEARCH AND TESTING OVERVIEW

The NTP's major long-term objective is the development, validation, and application of better, more specific, and less expensive test methodologies. Existing methodologies being examined include techniques to detect impaired immune, kidney, or pulmonary function, and neurobehavioral toxicity. New areas for methods development and validation include *in vitro* teratology, as well as short-term tests for presumptive carcinogenic potential. The largest single area of test methods dvelopment and validation is in cellular and genetic toxicology, where emphasis is placed on both *in vitro* and *in vivo* test systems for measuring somatic mutations, chromosome aberrations, aneuploidy, heritable mutations, cellular transformations, and DNA damage and repair. In the short-term, however, major emphasis is placed on toxicology testing activities.

Toxicology research and testing activities are divided into four major program areas: cellular and genetic toxicology (mutagenesis); carcinogenesis; toxicologic characterization; and reproductive and developmental toxicology (fertility and reproduction).

The major research, test methods development, and testing activities in FY 1984 and FY 1985 are briefly summarized below. (More detailed descriptions of specific program activities are given in the following chapters.)

Cellular and Genetic Toxicology -- NTP emphasizes an integrated research and testing program allowing evaluation of the genetic toxicity of chemicals to which humans may be exposed; developing an understanding of the mechanisms of cellular and genetic toxicity to provide a better basis for test interpretation and further test system development; and using test data to select chemicals, to set priorities for further testing, and to aid in the design and interpretation of long-term animal carcinogenicity and toxicity studies.

In FY 1984, NIEHS completed tests on 196 chemicals in *Salmonella* assay systems. Testing for heritable genetic effects was completed on 37 chemicals in *Drosophila*, and for cytogenetic effects on 79 chemicals in cultured mammalian cells (Chinese hamster ovary). Testing was completed on 84 chemicals in the L5178Y mouse lymphoma cell mutation system. In FY 1985, testing will continue at levels of about 200 completions in *Salmonella*, 60 in *Drosophila*, about 100 in Chinese hamster ovary cells, and 100 in L5178Y mouse lymphoma cells. Urine samples from rats will be tested for mutagenic activity of up to 15 chemicals a year.

In addition, a comprehensive *in vitro* short-term testing capability is being used to set priorities for further testing and to develop a data base for a spectrum of genetic toxicities. Between 20 and 30 chemicals were tested in FY 1984 in each of four classes of tests: (1) gene mutations in bacteria and mammalian cells; (2) chromosome effects in mammalian cells; (3) mammalian cell transformation; and (4) DNA damage/repair. Up to 40 chemicals will be evaluated in FY 1985.

Test methods development and validation activities at NIEHS include continuation of a dual laboratory evaluation of three mammalian cell transformation systems -- primary Syrian hamster embryo (SHE) cells, and two viral mediated transformation systems (SHE cells infected with Simian adenovirus 7, and rat cells infected with Rauscher leukemia virus). Validation will be started on two test systems in *Drosophila* and one in yeast for induction of aneuploidy. A cross-species comparison is being conducted to evaluate the capability of primary liver and bladder cells to activate precarcinogens of various chemical classes to mutagenic metabolites.

In vivo mammalian somatic cell test system development includes: mouse bone marrow cytogenetics; development and standardization of a protocol for assessing frequencies of chromosome aberrations and sister-chromatid exchanges in human lymphocytes and application of the protocol to select population groups; and evaluation of the utility of the mouse erythrocyte micronucleus assay as an adjunct to the prechronic toxicity testing phase in rodents. Additional studies include development of assays to detect chemically-induced gene transpositions in *Drosophila* and mammalian cells. Efforts at measuring germinal mutations in mice and providing cross-test comparisons among the morphological specific locus assay, the biochemical specific locus assay and the heritable translocation assay continue. Special applied studies continue to identify and characterize the mutagens produced by the cooking of various foods using both *in vitro* and *in vivo* short-term tests. Continuing research with *Salmonella* tester strains, yeast (*Saccharomyces*), and *Drosophila* is aimed at improving their value as test systems and gaining better understanding of mutational processes, including the relationship between DNA damage/repair and mutagenesis.

At NCTR, developmental work on heritable translocation capability has been completed. An NCTR-NIEHS project using the primary hepatocyte/DNA repair system to detect the potential genotoxicity of selected NTP chemicals continued, with forty coded chemicals evaluated in FY 1984. Forty more will be evaluated in FY 1985.

The NIOSH program, directed at assessing genotoxic risks in the workplace, included efforts in FYs 1984 and 1985 to: (1) further evaluate the arabinose resistant (Ara^r) assay system of *Salmonella* for sensitivity and application to worksite chemicals and mixtures; (2) further evaluate and field test methodologies for an *in situ* mutagenic monitoring system; and (3) complete the laboratory phase of a urine mutagenesis assay.

Carcinogenesis Research and Testing -- At NIEHS, the experimental design continues to be tailored to meet the special testing needs identified for each chemical. A typical protocol employs both sexes of mice and rats, and administration of multiple doses (usually three, plus vehicle and/or untreated concurrent controls) of the test chemical to groups of at least 50 animals for approximately two years. Dose ranges for the chronic study are based on estimates of maximum non-lethal minimally toxic doses (derived from prechronic studies), dose-response curve slopes, pharmacokinetic considerations, probable levels of human exposure and other relevant factors. In addition to the two-year exposure groups, some animals are killed after 15 months of exposure to evaluate chronic toxicity before the onset of senescent changes.

During FY 1984, the *ad hoc* scientific peer review panel associated with the NTP Board of Scientific Counselors approved technical reports on the 13 chronic studies completed during the year. New categories adopted by the NTP in FY 1983 were used in the reports to describe the strength of evidence for each individual study result. Data audits were completed prior to peer review for all the studies and no data discrepancies were found that would influence final interpretation. There were 21 chemical studies in the prechronic phase of toxicology and carcinogenesis testing and 169 chemical studies in the chronic phase at the end of FY 1984. There are 31 chemical starts projected for the prechronic phase of toxicity testing and 21 starts in the chronic phase in FY 1985. It is projected that 21 two-year toxicology and carcinogenesis studies are expected to be completed through the in-life phase of toxicity testing in FY 1985.

With respect to research and methods development activities, efforts were continued to refine short-term rat liver tumor models. The aim is to use these models to assess the relative initiating and promoting activities of rodent hepatocarcinogens. New initiatives in FY 1984 and 1985 include a study to explore the possible relationship of dietary oil or oil used as a vehicle for gavage studies and pancreatic cancer, and the influence of moderate to severe dietary restriction on background tumor rates. NIEHS will also begin a major initiative to better characterize the toxicity, using current animal testing methods, and to expand the data base for 25 chemicals for which convincing evidence exists linking exposure to development of human cancer.

At NIOSH, prechronic, long-term, and special studies aimed at elucidating the etiology of cancer in the workplace included: short asbestos fibers, silica, Min-U-Sil, pyrolysis effluents from foundry molds, and foundry-mold aggregates, administered intratracheally; Acid Black 52 and Disperse Yellow 3, administered intratracheally and in the diet; and roofing asphalt and coal tar pitch condensates, topically applied. NIOSH and NIEHS also continued collaboration on evaluation of a tumor promotion assay in V79 cells.

The NCTR program conducts prechronic and chronic toxicology and carcinogenesis evaluations on feed additives, animal or human drugs, pesticides, and other chemicals of interest to the FDA that were nominated for NTP testing. Included in FY 1984 was a study examining the relationship between chemical structure and toxicologic endpoints for a series of structurally similar antihistamines.

Toxicologic Characterization -- NIEHS continues placing emphasis in two major areas: (1) general toxicology, identifying the toxicity of a chemical by species, sex, dose, and, at least presumptively, by organ or organ systems affected; and (2) specific and more in depth characterization of toxicologic effects on the immunological, neurobehavioral, pulmonary, reproductive, and other tissues or organ systems. General toxicology is an important component of the prechronic testing phases (primarily 14-day and 90-180-day experiments). Applied with most chemicals being considered for long-term testing are a group of *in vitro* genetic toxicology assays and chemical disposition/pharmacokinetics studies. Morphological assessment -- including tumor pathology, toxicologic pathology, experimental pathology and clinical pathology -- is an essential component of toxicologic characterization of a chemical.

With regard to toxicology of major organ systems, emphasis in renal toxicology is placed on characterizing functional impairment produced by nephrotoxicants, and their pathophysiologic basis. A new effort in FY 1984 concerns chemical toxicity to the hematopoietic system in rats and chemical leukemogenesis. Studies in biochemical toxicology are concerned with characterizing changes in enzyme systems in the liver and other tissues after exposure to environmental chemicals. These enzymes metabolize chemicals and drugs to both inactive and toxic metabolites. Efforts in cutaneous toxicology include developing protocols that will optimize the design of prechronic and chronic tests by the dermal route, standardizing and reducing variability of the mouse skin initiation/promotion assay, and developing better methods for measuring dermal absorption of chemicals both *in vivo* and in an *in vitro* system. A number of chemicals of interest to the NTP were screened in the immunotoxicology assay panel for their ability to alter immune functions and/or host resistance to challenge. Research efforts focus on elucidation of general immunotoxic mechanisms. Research in neurobehavioral toxicology seeks to characterize in an animal model, the behavioral and neurobehavioral toxicity of chlordecone and to elucidate the mechanisms by which chlordecone and other organochlorine chemicals produce their neurotoxic effects.

Most chemicals chosen for long-term toxicity testing undergo some degree of chemical disposition evaluation. A number of such chemicals were evaluated in FY 1984. Several studies centered on investigating the effects of body composition and route of administration, especially gavage or dermal routes, on chemical disposition. Several other studies were initiated to determine whether greater than additive toxicity observed with binary combinations of chemicals is due to altered metabolism and disposition. Also begun in FY 1984 was an initiative evaluating the effects of increasing age on the metabolism, disposition and toxicity of chemicals.

Special toxicological studies to evaluate chemical classes continued in FY 1984. In the benzidine dye initiative, all planned chemical disposition and genetic toxicology studies were completed in FY 1984 while two-year toxicology and carcinogenesis studies were initiated on the benzidine congeners and selected derived dyes. Studies continued on selected ortho phthalic acid esters including chronic toxicity, reproductive toxicity, metabolism, dermal absorption and mechanistic studies. A new initiative is concerned with studying mechanisms of cellular toxicity of metals as part of prechronic toxicity testing. Other chemical classes being studied are psoralens, furans and flame retardants of diverse structure. As part of the Superfund project, a number of chemicals are being evaluated for chronic toxicity, mutagenicity, effects on fertility and reproduction, and for chemical disposition.

At NIOSH, toxicologic characterization studies continue to focus on pulmonary toxicology and neurobehavioral toxicology. In FY 1984, further comparisons were made with specific compounds in order to assess the relative sensitivity of pulmonary function tests and morphologic indices for detecting respiratory disease in animals. A primate model was used to evaluate the asthmagenic potential of vanadium pentoxide; a model for phthalic anhydride will be investigated. A new primate model was developed to evaluate agents for chronic byssinotic effects. NIOSH continued evaluating methods for assessing human neurotoxicity from chemicals, and will validate them in the NIOSH worksite program. Behavioral teratology studies will continue with a series of alcohols and aliphatic hydrocarbon solvents. In cutaneous toxicology, an *in vivo* method for directly quantitating percutaneous absorption of volatile chemicals in rodents was established and the quantitative absorption of several chemicals was studied. Analytical procedures were developed for measuring several metals and organic solvents in biological fluids, and were then applied to monitoring urine, blood and exhaled air from workers exposed to the chemicals.

At NCTR, detailed chemical disposition studies continue with gentian violet and will be completed in FY 1985 on sulfamethazine, chemicals that have been undergoing concurrent chronic toxicity testing.

Reproductive and Developmental Toxicology -- These programs range from conventional teratology testing through development of methodology for behavioral effects, male and female reproductive toxicity and postnatal toxicology, to mechanistically oriented studies. In the NCTR program in FY 1984, 13 conventional teratology studies on eight chemicals were completed, and an additional six studies on four chemicals were in progress. Selection of chemicals is coordinated with selection of chemicals for and results of the short-term *in vivo* reproductive toxicity assay and sperm morphology/vaginal cytology assays. Statistical analyses of the data from the interlaboratory collaborative behavioral teratology study will be completed during FY 1985.

At NIEHS, fertility assessment by continuous breeding is designed to evaluate two generations exposed to the test chemical, concentrating on effects on fertility and offspring assessment. Chemicals tested or under test have been from the glycol ether, polyglycol, phthalate ester, and methyl xanthine classes as well as miscellaneous chemicals. Sperm morphology and vaginal cytology evaluations have become a standard part of prechronic toxicity testing. Detailed morphological and biochemical studies were done on testicular toxicity of several chemicals. *In vitro* models of testicular toxicity will be examined in FY 1985. The lactational process is being studied as a source of exposure of neonates to chemicals with resulting toxicity. Studies have been initiated on the interactions of different halogenated hydrocarbons and their ability to alter normal development. In *in vitro* teratology test development, two cell culture systems are being evaluated as indicators of teratogenic potential.

In the NIOSH program, continuing experience with the short-term *in vivo* reproductive toxicity assay indicates that it is an appropriate method for developing data helpful in establishing further testing priorities. Investigations continued on the reproductive and developmental toxicity of glycol ethers, and a dermal teratogenicity study was completed. Inhalation reproductive toxicity studies continued on a series of industrial alcohols with the focus on teratogenesis. Inhalation studies are being expanded in FYs 1984 and 1985 to include other NTP priority compounds and to broaden the assessment toward a complete overview of male and female reproductive toxicity. A short-term teratology screening method in *Drosophila* is being evaluated with as many as possible of a select list of chemicals chosen for *in vitro* teratology test validation. Methods are being developed for studying functional teratology of the heart.

CELLULAR AND GENETIC TOXICOLOGY

NIEHS Cellular and Genetic Toxicology Branch

-Extramural Projects
  -Testing Projects
    -*In Vitro* Testing for Mutational and Chromosomal Effects............38
      -Microbial Mutagenesis Testing..................................38
      -Testing the Urine of Rats for Mutagenic Activity..............38
      -*Drosophila* Mutagenesis Testing...............................39
      -*In Vitro* Mammalian Cell Mutagenesis..........................39
      -*In Vitro* Cytogenetics in Mammalian Cells.....................40
    -*In Vitro* Multiple Test Systems.................................41
      -Coordinated Testing Project....................................41
    -Data Systems and Their Utilization...............................43
      -Genotoxicity Data Evaluation and Analysis......................43
      -Environmental Mutagen Information Center.......................44
  -Test Method Development and Validation Projects
    -*In Vitro* Assays..44
      -*In Vitro* Mammalian Cell Transformation.......................44
      -Aneuploidy Test Systems..46
      -*In Vitro* Assay for Promoters.................................46
      -Cell-Mediated Mutagenesis......................................46
      -Development of Human Cell Assay Systems for Genetic Toxicity...47
    -*In Vivo* Mammalian Somatic Cell Test Systems....................48
      -Mouse Bone Marrow Cytogenetics.................................48
      -Human Lymphocyte Cytogenetics..................................49
      -Mouse Erythrocyte Micronucleus Assay...........................49
    -Gene Transposition Assays..50
      -Chemically Induced Transposition in *Drosophila*...............50
      -Mouse Endogenous Retroviral Long Terminal Repeat (LTR) Elements for Studying Gene Transposition in Environmental Carcinogenesis...51
    -Special Application..52
      -Mutagens formed from the Cooking of Foods......................52
    -Heritable Effects - Mammalian Assays.............................53
      -Mouse Morphological Specific Locus Assay.......................53
      -Mouse Biochemical Specific Locus Study.........................54
      -Mouse Heritable Translocation Testing..........................55
    -Collaborative Activities...56
      -Collaborative Study on Short-Term Tests........................56
-Intramural Program
      -*Salmonella* Mutagenesis Research..............................57
      -Molecular Mechanisms of Recombination and DNA Repair in Yeast..58
      -Molecular Genetics of Meiosis and Mutagenesis in Yeast.........59
      -DNA Repair and Mutagenesis in *Drosophila*.....................60
      -Mammalian Cell Molecular Genetics..............................61

NCTR Division of Mutagenesis Research

      -Utilization of the Primary Hepatocyte/DNA Repair System to Detect Potential Genotoxicity of NTP Chemicals...90

NIOSH Division of Respiratory Disease Studies
- Validation of the Arabinose Resistant Assay....................92
- Methodology for Workplace Mutagenic Monitoring.................92
- Mutagenic Monitoring for High Risk Workers....................92
- Evaluation of Urine Mutagenesis Assay.........................92
- *In Vivo* and Partial *In Vivo* Cytogenetic Studies...............93

The cellular and genetic toxicology programs at the three NTP agencies have some parallel objectives. The NIEHS, through its Cellular and Genetic Toxicology Branch, is involved in development, improvement and validation of short-term tests for mutagens and carcinogens, using short-term tests to detect and characterize chemicals that may pose carcinogenic or genetic risks to humans, and in basic research on mutagenesis and related genetic effects of chemicals.

The NCTR program is focused on developing and validating *in vitro* and *in vivo* systems for determining genotoxicity of chemicals, and on using the primary hepatocyte DNA repair system to detect potential DNA damage induced by chemicals selected by the NTP.

NIOSH is concerned primarily with assessing genotoxic risks at the workplace and developing and using suitable assay systems for monitoring workers for the presence of genotoxic substances or the occurrence of genotoxic events.

NIEHS CELLULAR AND GENETIC TOXICOLOGY BRANCH

The major goal of the Cellular and Genetic Toxicology (CGT) Branch is to provide an integrated research and testing program using a variety of test systems to evaluate the genetic toxicity of chemicals to which humans may be exposed. The program is also aimed at developing an understanding of the mechanisms of cellular and genetic toxicity to provide a better basis for further development of test systems and interpretation of test results. Emphasis is currently placed on tests that measure mutagenicity in bacteria, and mutagenicity and aneuploidy in yeast and *Drosophila* as well as mutagenicity, DNA damage, chromosomal changes, and neoplastic transformation in mammalian cells. Test data will be used to select chemicals and to set priorities for further testing and to aid in the design and interpretation of long-term animal carcinogenicity and toxicity studies.

An implicit goal of the cellular and genetic toxicology effort is to establish a scheme of short-term testing that can be used to predict carcinogenicity and germ cell as well as somatic cell mutagenicity of chemicals, and, thereby, reduce the need for *in vivo* assays, or to assist in setting testing priorities for long-term animal assays. However, for short-term tests to be predictive, several criteria must be fulfilled. These include a knowledge of the reproducibility of individual test results, the accuracy with which test results from single or multiple tests predict a toxic effect *in vivo*, and the relationship of the *in vitro* endpoint measured to *in vivo* carcinogenicity, mutagenicity, or other manifestations of toxicity. The application of a group of complementary tests that meet these criteria may ultimately result in an effective system for testing chemicals. An important part of the Branch program is to produce sufficient short-term test data, particularly across chemical classes, to establish the accuracy with which one can predict carcinogenic effects in animals. Even with the appropriate use of available test systems, some potential carcinogens (or cocarcinogens or tumor promoters) may not be identified, particularly those that do not induce damage leading to observable gene mutations or chromosomal changes. Therefore, it is important that we continue to develop new methods that are capable of detecting carcinogens that are not identified by the assays currently in use and to identify chemicals that "promote" tumor development. In order to accomplish these goals, it is important that the program remain involved in, and responsive to, basic research developments.

A substantial portion of Branch resources are committed to studies of chemically induced mutations. These mutation studies can be divided into two categories: somatic cell and germ cell. The major difference between the two is that mutations arising in germ cells can be transmitted to subsequent generations, while somatic cell mutations are expressed only in the affected individual. A chemical that is mutagenic in somatic cells may have the potential to be mutagenic in germ cells. Conversely, germ cell mutagens are likely to be somatic cell mutagens.

The portion of the program concerned with validation of assays and the testing of chemicals is performed primarily through extramural contracts and interagency agreements; however, basic research, the development or modification of tests, and the management and analysis of data are generally performed within NIEHS.

The key extramural contract activities include: mutagenesis testing in Salmonella, Drosophila, and mammalian cells; measuring chromosome aberrations (CAs) and sister-chromatid exchanges (SCEs) in cultured mammalian cells; the development and evaluation of an in vivo assay to detect cytogenetic damage; the development of assays for induction of aneuploidy in yeast and Drosophila; an in vitro assay in mammalian cells for induced DNA damage; and an evaluation of three mammalian cell transformation systems, including Syrian hamster embryo (SHE) cells, SHE cells infected with Simian adenovirus (SA7), and retrovirus-infected rat cells. (The latter two systems measure chemical enhancement of viral transformation or viral-mediated transformation.) Additional studies include the development of assays to detect chemically induced gene transposition in Drosophila and mammalian cells and to develop or obtain a human cell system that can be used to test the genetic toxicity of chemicals.

A coordinated testing effort is being conducted to assess the genetic toxicity of likely candidates for long-term toxicology studies. The coordinated effort is also being used to acquire test results from several short-term tests on a group of carcinogens and, in particular, noncarcinogens to determine better the ability of individual and multiple short-term tests to predict carcinogenicity in rodents.

Other projects include an effort to develop a standardized protocol by which the frequencies of CAs and SCEs can be accurately and reproducibly measured in human lymphocytes with particular emphasis on understanding the sources of variation that may affect the measurement of these endpoints. The measurement of chemically induced germ cell mutations in mice is being done by both the morphological and biochemical specific-locus assays. Other developmental projects include analysis of mutagens produced in cooked foods and an attempt to develop an assay for chemically induced transpositions of specific DNA sequences in Drosophila.

Intramural research efforts involve both prokaryotes and eukaryotes. Studies using Salmonella typhimurium include attempts to increase our understanding of the Salmonella mutagenicity test system, to improve the sensitivity and efficiency of protocols currently in use, and to use the Salmonella test as a tool to study in vitro and in vivo metabolism of mutagenic chemicals.

Two aspects of meiotic development are being studied using the yeast Saccharomyces cerevisiae as a model genetic and biochemical system. The first concerns the role of DNA repair mechanisms in meiosis; several mitotically defined repair genes are essential in normal meiotic/germinal processes. The second involves identifying those gene functions that are specific to meiosis. Both repair- and the meiotic-specific genes are being isolated, and their role during meiosis, particularly recombination, is being examined. Yeast systems are also being developed to examine chromosomal and gene mutagenesis and the role of DNA repair systems using defined centromere and expressed gene sequences. The genetic control of DNA repair and mutagenesis is also being studied in Drosophila melanogaster.

Oncogenesis by transposable elements is being studied in spontaneous and radiation-induced hematopoietic neoplasms of the RFM/Un mouse. This model system is based on the somatic reintegration in certain neoplastic phenotypes of the endogenous ecotropic provirus present in the genome of this mouse strain. In order to test the "downstream promotion" mechanisms of oncogenesis, somatically acquired provirus integration sites have been cloned and analyzed. The long-range goal of this project is to identify the genetic targets, possibly oncogenes, that are involved in the development of specific neoplastic phenotypes.

The problem of organ and species specificity of chemical carcinogens is being studied by measuring the production of mutagenic metabolites from primary epithelial cells (activator cells) of liver, lung, and urinary bladder of different species. The activator cells are cocultivated with target cells (V79 hamster cells or Salmonella) to measure toxicity, SCEs, and mutation. Long-range plans include development of systems to measure chemically induced multiple genetic endpoints in human cells.

EXTRAMURAL PROGRAM
FY 1984 ACCOMPLISHMENTS AND FY 1985 PROGRAM PLANS

TESTING PROJECTS

- In Vitro Testing for Mutational and Chromosomal Effects

Microbial Mutagenesis Testing -- The *Salmonella* microsome test developed by Ames and his coworkers is used as an initial screen for mutagenic chemicals. Mutagenicity is assayed with *Salmonella typhimurium* tester strains TA97, TA98, TA100, and TA1535 using a modification of the *Salmonella* microsome assay in two laboratories (Microbiological Associates, Dr. S. Haworth; and SRI International, Dr. K. Mortelmans). All chemicals are incubated with tester strains in suspension prior to addition of soft agar and plating for detection of induced revertants. Exogenous metabolic activation is provided by liver homogenates (S-9) from Aroclor 1254-induced Sprague-Dawley rats and Syrian hamsters. All chemicals are tested under code at five doses, in triplicate, in each strain of *Salmonella*, then are retested at least one week after the first test. Results are entered directly into minicomputers at the testing laboratories for transfer to the NIEHS data-base system. Results have been received from these laboratories on a total of 1255 test samples encompassing 1007 unique chemicals. In FY 1984, tests were completed on 196 samples. These results are listed in Table 1. These results represent preliminary evaluations of test data, are therefore subject to revision, and should not be used as definitive results.

Chemicals that are positive for mutagenicity, or that produce equivocal responses in *Salmonella*, are analyzed for identity and purity. The *Salmonella* results are used, along with other toxicology data, by the NTP to assist in making decisions regarding further testing of the chemicals, and by NTP chemical managers as additional information pertinent to the evaluation of chronic studies. The *Salmonella* data are also used in the selection of chemicals for additional *in vitro* and *in vivo* genetic toxicology studies.

FY 1985 PROGRAM PLANS

In FY 1985, 200 tests are scheduled to be completed in *Salmonella*; most of the chemicals to be tested will be selected from the list in Table 2. Some of these chemicals may not be tested due to unavailability, high cost, or for other reasons, while other chemicals may be added in response to NTP or other agency needs. As a part of this program, a new contract will be awarded, in early FY 1985, to provide for the testing of approximately 25 chemicals/year using protocols other than the one used in the ongoing contracts. This additional contract is needed because a number of chemicals which are not mutagenic in the standard protocol may be mutagenic when tested by modified protocols; for example, allowing for reductive metabolism, or exposing the cells to the test chemical vapor in a sealed chamber. In this new contract, the protocols to be used will be defined according to the chemical being tested and the purpose of the test. Results of all tests completed to date wil be submitted for publication. (CONTACT PERSON: Dr. E. Zeiger)

Testing the Urine of Rats for Mutagenic Activity -- The *Salmonella* test using rat urine offers an opportunity to determine whether or not mutagenic urinary metabolites are produced from chemicals being administered daily to rats.

Chemicals selected for evaluation will be from those on 14-day prechronic test or from those currently on the two-year chronic test. If positive results are obtained in the urine assay, these results will be compared to the in vitro Salmonella preincubation test and evaluated with respect to whether or not the urinary mutagen(s) are free and direct acting, are conjugated with other substances, and/or require metabolic activation. (Negative results in the urine assay cannot be extrapolated further.) The mutagenicity results will also be evaluated against any chemical disposition data available on the test chemicals. This will provide information on the ability of the rat to metabolize the test chemical to a mutagen in vivo, as well as preliminary information regarding the activation and/or detoxification of the chemical. The results from these assays will demonstrate the capability of the urine assay to detect chemicals administered to rats in the food or by gavage.

FY 1985 PROGRAM PLANS

A contract will be awarded to test rat urine samples (up to 15 chemicals/year) for mutagenic activity. (CONTACT PERSON: Dr. E. Zeiger)

Drosophila Mutagenesis Testing -- The sex-linked recessive lethal test, which measures both gene and chromosome mutations, and the reciprocal translocation test, which measures chromosome breakage and rejoining in Drosophila melanogaster, are being used to screen chemicals for mutagenicity in two laboratories (Brown University, Dr. S. Zimmering; and University of Wisconsin at Madison, Drs. R. Valencia and S. Abrahamson). Chemicals are selected based, in part, on results obtained from previous mutagenicity and genotoxicity tests using Salmonella and Chinese hamster ovary cells, and in part on interest for the carcinogenesis bioassay. Chemicals are administered by feeding for the sex-linked recessive lethal test. If the results are negative, the test is repeated using injection; if the results are again negative, the chemical is considered nonmutagenic in Drosophila for this endpoint. If the results are positive, the chemical is tested in the reciprocal translocation test using the means of administration which gave the positive result. In the reciprocal translocation test, sperm are stored to enhance the ability to recover chromosome breaks induced by the chemicals. Results from both tests are entered on data forms and transferred to a computerized data base system. Results for FY 1984 are given in Table 3. These results represent preliminary evaluations of test data, are therefore subject to revision, and should not be used as definitive results.

FY 1985 PROGRAM PLANS

It is anticipated that 60 samples will be tested during the fiscal year. Many of the chemicals will be selected from the list in Table 4. Many of the samples will be tested using larval feeding as the route of administration in order to compare this procedure with others that have been used in the past. This comparison is of interest because larvae have a different array of metabolic activation enzymes than adults and may be able to activate a different set of promutagens. (CONTACT PERSON: Dr. J. Mason)

In Vitro Mammalian Cell Mutagenesis -- A study designed to evaluate the ability of the L5178Y mouse-lymphoma cell-mutation assay to detect the mutagenic activity of chemicals with diverse chemical structures was analyzed. The study included development of a common protocol, of quality control standards, of response categories based on mathematically defined criteria, and determination of inter- and intralaboratory reproducibility under large-scale test conditions. Methods of data handling and analysis, including statistical support, were explored so that the large volume of data generated by this study could be handled efficiently and consistently.

Based on the results of this study, the successful development of a working protocol and an effective data management system, two laboratories (Litton Bionetics, Inc., Dr. Brian Myhr; and Inveresk Research International, Dr. Douglas McGregor) are each testing 50 chemicals per year for their mutagenic activity in a mammalian cell system. In addition to this primary goal, the laboratories are also optimizing the exogenous metabolic activation system used in these studies, analyzing the mouse lymphoma cells for their endogenous ability to activate chemicals of different chemical structure, and examining the relative sensitivity of different loci. In accordance with this latter goal, a limited number of chemicals have been identified which are positive in the mouse lymphoma assay but negative in all or most other genetic toxicity tests. Most of these compounds are also positive in long-term animal studies. These compounds will be tested in another mammalian mutagenesis assay system to see if the mouse lymphoma results can be verified. Results for chemicals tested in FY 1984 are given in Table 5. These results represent preliminary evaluations of test data, are therefore subject to revision, and should not be used as definitive results.

One characteristic of the mouse lymphoma assay is that the mutant colonies consist of large and small colonies. It has been reported that the small colonies have a high frequency of chromosomal aberrations, though this hypothesis has not been confirmed. At SRI International, Drs. A. Mitchell, C. Rudd, and W. Blazak, are investigating the causes of the bimodal size distribution of trifluorothymidine resistant (TFT^r) colonies from control and mutagen-treated cultures. They have confirmed that small colony populations do carry chromosomal aberrations at chromosome 11 which contains the TK gene.

FY 1985 PROGRAM PLANS

It is projected that testing will be completed on 100 chemicals in the mouse lymphoma cell system in FY 1985. Most of the chemicals to be tested will be selected from the list in Table 6. In addition, the effort to understand the causes of small colony formation in the mouse lymphoma system will continue. (CONTACT PERSON: Dr. W. J. Caspary)

In Vitro Cytogenetics in Mammalian Cells -- Chromosome aberrations (CAs) and sister chromatid exchanges (SCEs) are used as indicators of genetic toxicity of chemical agents. While the literature is extensive on the nature of cytogenetic events and the effects of particular chemicals, there have been few attempts to develop a highly reliable and reproducible in vitro system for detecting chemically-induced cytogenetic damage. A protocol using cultured Chinese hamster ovary (CHO) cells was developed and validated previously in a dual laboratory study. Testing of chemicals during FY 1984 was conducted by two laboratories (Environmental Health Research and Testing, Inc., Dr. D. Gulati, and Litton Bionetics, Inc., Dr. J. Ivett). A third laboratory (Bioassay Systems, Inc., Dr. K. Loveday) will also be participating in the testing of chemicals. The total capacity for testing among all three laboratories will be approximately 100 chemicals per year.

Testing was completed on 79 chemicals in FY 1984. Results are presented in Table 7. These results represent preliminary evaluations of test data, are therefore subject to revision, and should not be used as definitive results.

FY 1985 PROGRAM PLANS

Testing of chemicals will continue at a rate of approximately 100 chemicals per year among the three laboratories. Most of the chemicals to be tested will be selected from the list in Table 8. A description of the statistical methods, test protocol, and supporting data from control experiments will be published. Results obtained with over 100 chemicals will also be published. (CONTACT PERSONS: Dr. E. Zeiger, Dr. M. A. Resnick, and Dr. M. Shelby)

- *In Vitro Multiple Test Systems*

Coordinated Testing Project -- This project was designed to provide genetic toxicity data to aid in setting priorities for long-term testing of chemicals undergoing prechronic toxicity testing and to provide pertinent genetic toxicity information as needed for use by the NTP experimental design groups. The scope has been expanded to include evaluation of chemicals for which long-term studies in rodents have been completed, thus, providing a data base on genetic toxicity with particular emphasis on chemicals found to be noncarcinogenic in rodent two-year studies. One goal of the Coordinated Testing Project is to test 50 of these chemicals in all four classes of genetic toxicity tests by the end of FY 1985. In addition, an evaluation of genetic toxicity will be conducted on a limited number of chemicals already committed to two-year testing. These results will provide a comprehensive data base on the genetic toxicity potential of a diverse group of chemicals.

A comprehensive *in vitro* short-term testing capability developed through program contracts and interagency agreements with EPA and NCTR uses the following four broad classes of genetic toxicity assays:

Class I: Gene mutations in bacteria (*Salmonella*/microsome assay) and in mammalian cells (L5178Y mouse-lymphoma cell TK$^{+/-}$ forward mutation assay).

Class II: Chromosome effects in mammalian cells: The *in vitro* cytogenetics assay in Chinese hamster ovary (CHO) cells for detection of chromosome aberrations and sister chromatid exchanges.

Class III: Mammalian cell transformation assay:

a. The BALB/c-3T3 *in vitro* transformation assay.
A one-year interagency agreement was initiated with EPA in FY 1984 to perform the BALB/c-3T3 *in vitro* transformation assay on up to 30 chemicals. To increase sensitivity, the assay was modified to include a metabolic activation step by co-cultivation of the BALB/c 3T3 cells with primary rat hepatocytes. By the end of FY 1984, 28 chemicals had been tested in both the standard and modified transformation assays.

b. The enhancement of Simian adenovirus (SA7) transformation by chemical carcinogens using Syrian hamster embryo (SHE) cells. Twenty chemicals were completed in the assay by the end of FY 1984. Up to 25 chemicals will be tested in FY 1985.

c. Under a separate project (in vitro mammalian cell transformation) carcinogens and non-carcinogens are being evaluated in three different transformation systems in a multiple-laboratory coded compound study (see section on In Vitro Mammalian Cell Transformation). As part of the Coordinated Testing Project, chemicals which represent both NTP bioassay positive and negative chemicals are being tested in these three transformation systems in order to generate across-chemical and across-system data. This study (1) will permit the realization of an expanded data base of genetic toxicity on these chemicals which are representative of diverse structural classes, and (2) may determine what transformation system will be the most useful for the identification of potential carcinogens.

Class IV: DNA damage/repair:

a. The in vitro unscheduled DNA synthesis (UDS) in rat liver primary cell culture assay.

The induction of DNA repair, measured as UDS, in non-dividing cells has been shown to be a useful indicator of the genetic toxicity of chemicals. The assay employs primary cultures of rat hepatocytes and offers the advantage of a short-term test using metabolically competent target cells, thus eliminating the need for exogenous activation preparations. The evaluation of 40 chemicals was completed in FY 1984. An additional 40 chemicals will be tested in FY 1985.

b. The in vivo - in vitro UDS in rat liver primary cell culture assay.

The in vivo - in vitro hepatocyte DNA repair assay represents an important modification and extension of the in vitro rat hepato DNA repair assay because it involves the treatment of animals rather than the administration of chemicals directly to cells in culture, providing information on important in vivo factors related to uptake, metabolic activation, distribution, detoxification, and elimination. The in vivo - in vitro assay is known to be responsive to the genetic toxicity of some classes of chemicals, e.g., the nitroaromatics, to which the in vitro UDS rat primary hepatocyte culture assay does not respond.

Results from the two-year rodent bioassay clearly indicate that there are differences in sensitivity according to sex and species response to the chemical induction of tumors. In order to investigate possible species specificity in the in vivo - in vitro hepatocyte DNA repair assay, the test was also performed in mouse ($B6C3F_1$) primary hepatocytes.

> Some liver carcinogens (e.g., carbon tetrachloride) which do not express direct genetic toxicity appear to cause tumors by inducing hepatotoxicity (necrosis) and subsequent hepatocyte proliferation. Therefore, in vitro hepatotoxicity studies were performed on a limited number of chemicals in both rat (F344) and mouse ($B6C3F_1$) primary hepatocytes. Although only a small number of chemicals were tested in FY 1984 in both the DNA and hepatotoxicity assays, it appears that low molecular weight halogenated aliphatic compounds are more likely to be hepatotoxic than directly genotoxic in primary hepatocytes.

It is not intended that results from the tests described above be used to define the carcinogenicity of a chemical or its mutagenicity in an intact animal. Rather the results should provide a reasonable profile of the genetic toxicity of the chemical. Such information can be used in determining what additional testing or other experimental studies may be appropriate. At present, there is inadequate evidence to select a specific group of assay systems as a prescreen for carcinogens or mutagens. This group of assays should not be interpreted as NTP endorsement of any specific combination of biologically-based tests. These seven tests are among the most widely available in commercial testing laboratories. New test systems will be used to supplement or replace these existing tests if data sufficient to justify such changes become available. The results of this project should provide a state-of-the-art profile of the genetic toxicity of many chemicals of priority interest to the Program.

Between 20 and 30 chemicals were tested in each component of the four broad classes of genetic toxicity tests in FY 1984.

FY 1985 PROGRAM PLANS

It is planned to evaluate up to 40 chemicals for genetic toxicity in each test component of the four classes of genetic toxicity assays. In addition, the test components will continue to be evaluated to determine if testing protocols are in need of modification. (CONTACT PERSON: Dr. J. W. Spalding)

- Data Systems and Their Utilization

Genotoxicity Data Evaluation and Analysis -- Although the precise mechanisms by which chemical carcinogens cause cancer are not known, a substantial body of evidence indicates that the alteration of the genetic apparatus of a cell is a necessary step in chemical carcinogenesis. This notion is subsumed under the rubric of the "Somatic Mutation Theory of Cancer," which is currently a major working hypothesis regarding the way in which chemicals cause cancer. Studies over the last 10-15 years have indicated that most chemical carcinogens exhibit genetic toxicity. Because of the important connection between chemical mutagenesis and carcinogenesis, it was considered instructive to discuss and compare the mutagenicity of a chemical to its carcinogenicity.

A project (Oak Ridge Associated Universities, Dr. D. DeMarini) has been started: (1) to include the genetic toxicology data from the Cellular and Genetic Toxicology Branch (CGTB) and the associated literature in the NTP Toxicology and Carcinogenesis Technical Reports; and (2) to discuss the carcinogenicity of various chemicals in terms of the mutagenicity of such chemicals. The format, style, references, etc. needed to present the CGTB's genetic toxicology data have been developed. This includes tables to present Salmonella, in vitro cytogenetic, Drosophila, mouse lymphoma, UDS, and in vitro transformation data. These data are included in the Introduction of the Technical Reports; an analysis of the mutagenicity and carcinogenicity of the particular chemical is included in the Discussion section of the Report. So far, this information has been included in the Technical Reports of studies on: benzene, benzyl acetate, 1,3-butadiene, chlorodibromomethane, 2-chloroethanol, HC Blue 1, HC Blue 2, eugenol, fluorescein, 8-hydroxyquinoline, monuron, pyridine, Telone II (1,3-dichloropropene), tetrachloroethylene, trichloroethylene, tris-(2-ethylhexyl)phosphate, and witch hazel (Hamamelis water).

In addition, summaries of the genetic toxicology data from the literature and the CGTB have been prepared for chemical managers for their 90-day prechronic reports and for Toxicology Design Committee meetings. Some of these chemicals are: 9-aminoacridine, benzoyl chloride, bromobenzene, chloramine, benzethonium chloride, citral, N-nitrosodiethanolamine, triethanolamine, C.I. Direct Yellow, malonaldehyde, diallylphthalate, 1,2-dichloropropane, manganese sulfate, and nickel oxide.

FY 1985 PROGRAM PLANS

Summaries and analyses of genetic toxicology data from the literature and the CGTB will be included in all upcoming NTP Technical Reports, and in 90-day prechronic reports. (CONTACT PERSON: Dr. M. D. Shelby)

Environmental Mutagen Information Center -- The Environmental Mutagen, Carcinogen, and Teratogen Information Program (EMCTIP), located at the Oak Ridge National Laboratory (ORNL), receives funding from the NTP to maintain the Environmental Mutagen Information Center (EMIC) file. The EMIC file is a data base that contains primarily published bibliographic information on chemicals, biological processes or physical agents that have been tested for mutagenicity. Each data entry is indexed on bibliographic information, on one or more biological endpoints, and on a range of technical data that allow for inquiries according to specific areas of interest. As of September 30, 1984, the EMIC file, which is available on DOE/RECON (at ORNL), contained 52,146 records on 17,973 unique chemicals, biological processes or physical agents. The EMIC file available on NLM/TOXLINE contained 43,721 records and is updated on a quarterly basis. The staff at EMCTIP are available to aid NTP staff in specialized searches and to answer questions on the use of the file. (CONTACT PERSON: Mr. S. Stasiewicz, NIEHS)

TEST METHOD DEVELOPMENT AND VALIDATION PROJECTS

- In Vitro Assays

In Vitro Mammalian Cell Transformation -- For many classes of chemicals, there is a high concordance between the ability of the chemical to induce neoplastic transformation in certain mammalian cells in culture and the induction of tumors in vivo. Several cell culture systems, including primary cultures, continuous lines, and virus-infected cells, have been used to identify potentially carcinogenic chemicals. However, sufficient across-chemical and across-system data do not exist to permit an evaluation of which system or systems may be most useful, and to determine what characteristic advantages or limitations each system may have in the identification of potential carcinogens. Included among these are the BALB/c 3T3 cell line, which has been evaluated by the NTP and is being used in the Coordinated Testing Project, and the C3H 10T$\frac{1}{2}$ cell line, which is being evaluated through the Division of Cancer Etiology, NCI. Three other systems, including primary Syrian hamster embryo (SHE) cells, and two viral-mediated transformation systems (SHE cells infected with Simian adenovirus 7) (SA7), and rat cells infected with Rauscher leukemia virus (FRE/RLV), continue to be evaluated by the NTP in a multiple-laboratory, coded-compound study.

Current contract laboratories and principal investigators are: (1) SHE System: A. D. Little, Inc., Drs. A. Sivak and A. Tu; Microbiological Associates, Inc., Dr. R. Kouri; Argonne National Laboratory, Drs. E. Huberman and C. Jones; (2) SHE/SA7 System: Northrop Services, Inc., Dr. G. Hatch; Microbiological Associates, Inc., Dr. L. Schechtman; and (3) FRE/RLV System: Litton Bionetics, Inc., Drs. J. Poiley and R. Raineri; Northrop Services, Inc., Dr. W. Suk,; and Biotech, Inc., Dr. A. Steuer.

Major goals of this project have included: the standardization of a test protocol; identification of key test reagents and materials; selection of optimal lots of reagents and materials following preliminary testing; acquisition of sufficient quantities of critical reagents; and tests of representative transformation positive and negative chemicals (model chemicals) for toxicity and transformation to establish interlaboratory reproducibility of the methods. Each contract laboratory has the responsiblity of focusing on key components of the test system (e.g. identification of suitable frozen cell pools; identification of optimal serum and medium stocks). Progress has been made in all these areas, although some technical aspects require further evaluation. Preliminary toxicity and transformation assays of the model chemicals have been performed in all three laboratories, and the results are being used for determining the degree of interlaboratory reproducibility.

Other goals were: preparation of a publication by the laboratories detailing the results of work on model chemicals; establishment of working criteria for acceptability and evaluation of the assay; and resolution of any technical differences. Progress has been seen in all these areas and work is continuing. Additional basic research into the mechanisms of the assay, ways to enhance the assay's sensitivity, and to further define morphological criteria of transformation are required. Because of the difficulties encountered with various technical aspects of this assay, work has progressed at a slower rate than expected. Therefore, these contracts will be extended for an additional year so that there can be continuity in development and evaluation.

FY 1985 PROGRAM PLANS

Further evaluation of the current working protocols will be done using coded chemicals that have been tested in rodents by the NTP. There will be a great deal of overlap in the chemicals tested in the respective assays so that across-test and across-chemical comparisons can be made. Additional studies to improve the sensitivity and reproducibility of the assay systems and to understand better the mechanisms of chemical transformation or enhancement will be conducted. (CONTACT PERSON: Dr. R. W. Tennant)

Aneuploidy Test Systems -- Three systems are being developed for monitoring chemically-induced aneuploidy, a genetic endpoint for which reliable assays are not available. Two of these systems measure germinal, or meiotic, events in *Drosophila* (Brown University, Dr. S. Zimmering) and *Saccharomyces cerevisiae* (University of California at Berkeley, Dr. S. Fogel), and a third detects mitotic aneuploidy in *Saccharomyces* (Technichse Hochschule, Darmstadt, Federal Republic of Germany, Dr. F. Zimmermann). Several chemicals have been identified which consistently produce positive responses, and are serving as controls in further development. For purposes of comparison with other genetic endpoints, the systems also have the capability of monitoring chemical effects on recombination and mutation induction. These assay systems, in combination with other short-term tests, have the potential to improve the evaluation of chemically-induced genetic damage. The use of whole animal and single cell systems allows interspecies comparisons in terms of germinal events. Since the relevance and the mechanisms of mitotic and meiotic aneuploidy may differ, development of the two systems within the same organism should prove useful.

FY 1985 PROGRAM PLANS

The three contract laboratories are nearing the completion of the developmental plans, including strain and protocol development. The next phase is testing with agents that cause aneuploidy. Based on the resulting observations, it is expected that final protocols and methods of data analysis will be developed so that validation of the systems and testing with coded chemicals can begin. (CONTACT PERSONS: Dr. M. A. Resnick and Dr. J. Mason)

In Vitro Assay for Promoters -- The V79 cell metabolic cooperation assay is being evaluated in a joint project with NIOSH. The assay is based on the ability of chemicals with promoter activity to interrupt cell-to-cell transfer of low molecular weight metabolites. Twenty-five chemicals of known *in vivo* promoting or nonpromoting activity were test coded in a dual laboratory study. The data are being analyzed by NIOSH to determine the appropriate statistical methodology to be applied and the predictability of the system with respect to the chemicals tested to date. It is apparent from the data that several known promoters are active in the system. NIOSH and NTP will award competitively two new three-year contracts to further define and develop the system and to test up to 40 coded chemicals in dual laboratories.

FY 1985 PROGRAM PLANS

The results of the 1983-1984 study will be published in a peer reviewed journal. The two new contracts will be awarded to initially investigate variables such as pH effects, Ca^{2+} level effects, and the timing sequence of addition of 6-thioguanine and the promoting chemical. After about six months of system development in these areas, the laboratories will begin testing the coded chemicals. (CONTACT PERSON: Dr. R. J. Langenbach)

Cell-Mediated Mutagenesis -- Intact cells can be used as an exogenous metabolic activation system in many short-term assays for carcinogenic/mutagenic chemicals. Under an interagency agreement, the EPA is evaluating the capability of intact primary liver and bladder cells from various species (rat, hamster, dog, and bovine) for activating members of various classes of chemical carcinogens to metabolites mutagenic for Chinese hamster V79 cells and/or

Salmonella typhimurium. The work also focuses on identification of carcinogen metabolites and DNA adducts in the liver and bladder cells. Data obtained will be correlated with previously observed mutagenic responses. Such studies should provide insight into the biological basis of organ and species specificity of chemical carcinogens. In addition, several NTP priority chemicals are being tested for mutagenic activity in the bladder cell-mediated systems.

FY 1985 PROGRAM PLANS

The results of the study will be reported in the peer-reviewed literature. In FY 1985 the project will be conducted as part of the Principal Investigator's in-house research. (CONTACT PERSON: Dr. R. J. Langenbach)

Development of Human Cell Assay Systems for Genetic Toxicity -- Most long-and short-term assays for detection of potential human carcinogens use microorganisms, rodents, rodent cells, or rodent enzyme preparations to determine the carcinogenicity and/or genetic toxicity of chemicals. However, species differences in response to chemical carcinogens do exist, and therefore, the determination of the chemicals' genetic effects in human cells may be more relevant to its effect in humans. Human cell systems that can be used to screen for agents that cause genetic damage have been reported, but these systems require further development before they can be routinely used. Two possible approaches are being pursued.

One approach uses intact, freshly isolated human liver cells (from surgery or immediate autopsy) for metabolic activation and a human target cell line to measure genetic endpoints. Methodologies for freeze storage of hepatocytes to maintain metabolic capability have been reported, and when further developed, will allow use of stock cells from the same donor which could eliminate some problems with individual variation in liver metabolic capability. The individual variation in human liver carcinogen activation potential is a research area which itself will be further investigated.

The second approach is the development of a human cell system with metabolic activation of the chemical and induction of genetic damage within the same cell. However, it does require that the cells are capable of multiple cell divisions to manifest the genetic damage and that the metabolic capability of the cells is manifested so that a broad spectrum of chemical classes can be activated. The loss of xenobiotic metabolism capability with subculture or time in culture is significant and methods are needed to maintain or manipulate enzyme levels within the cells. Some methodologies which may be possible to enhance cellular metabolism include gene activation or induction of enzyme systems already present and/or appropriate gene transfer by DNA transfection or cell hybridization. Some of the human cell systems described to date, which are suitable for such studies, include liver cell lines, tumor cell lines from various organs and human lymphoblast lines. By manipulating the metabolic ability of these cells, they could become useful systems in genetic toxicity screening. A long-term goal of the approach is to develop human cell systems as genotoxicity assays and to compare human cell systems to rodent cell systems for predicting genetic hazard to humans.

Proposals are being evaluated, and it is anticipated that three laboratories will be awarded contracts in FY 1985.

FY 1985 PROGRAM PLANS

For the second or cell-mediated approach, techniques for isolating viable human hepatocytes and their co-cultivation with target human cells will be established. Conditions for measuring multiple genetic endpoints in the human cells will be determined. Human hepatocyte metabolism of four known carcinogens to genotoxic intermediates and to metabolites analyzable by chromatographic techniques will be conducted. From these studies, initial data on individual variation in human hepatocellular metabolism will be obtained.

For the genetic manipulations to increase metabolism of human cells, a cell system with reasonable metabolic capability will be chosen, and the chemical classes which the cells can and cannot metabolize will be determined. Metabolic activation of four known carcinogens will be assessed by induction of measurable genetic endpoints, and analysis of the metabolic potential of the cells will be initiated. (CONTACT PERSON: Dr. R. J. Langenbach)

- In Vivo Mammalian Somatic Cell Test Systems

Mouse Bone Marrow Cytogenetics -- Chromosomal aberrations (CAs) and sister-chromatid exchanges (SCEs) are among the genetic events induced by many chemical mutagens and carcinogens. The primary objectives of this study are to develop and assess a protocol for the simultaneous determination of these two endpoints *in vivo* in the same strain of mouse ($B6C3F_1$) used in NTP chronic toxicity studies and to test chemicals for their ability to induce cytogenetic damage in mice.

Through collaboration between two laboratories (Brookhaven National Laboratory, Dr. R. Tice; and Oak Ridge Associated Universities, Dr. A. McFee), a protocol has been developed for routine testing of chemicals for the induction of CAs and SCEs in mice. In addition to complementing *in vitro* genotoxicity test results by providing an *in vivo* test for genetic toxicity, comparisons of findings with results from chronic carcinogenesis studies may permit a better understanding of the relationship between induced cytogenetic effects and tumor induction.

The protocol was used to test four coded chemicals in both laboratories, and results were in agreement in seven of the eight possible (four chemicals x two endpoints) results. Dichlorvos was negative and ethyl methanesulfonate was positive for both end-points in both laboratories, benzo(a)pyrene gave positive SCE and negative CA results, and 2-acetylaminofluorene was positive for SCE in both laboratories but positive in only one laboratory for CA. Studies to resolve this difference are under way.

FY 1985 PROGRAM PLANS

Results of the protocol studies and the two-laboratory coded compound study will be published. Ten chemicals selected from among those of primary interest to the NTP will be tested in each laboratory for *in vivo* cytogenetic effects. Most will be those scheduled for chronic toxicity testing in rodents. (CONTACT PERSON: Dr. M. D. Shelby)

Human Lymphocyte Cytogenetics -- The measurement of chromosomal damage in peripheral lymphocytes offers a practical means of detecting exposures of humans to genotoxic agents. The basic technique has been used for many years to detect and quantify human exposure to ionizing radiation. It has recently been applied to a lesser extent to detect exposures to chemical agents. Differences in protocols used in these cytogenetic studies on persons exposed to chemical agents have often precluded cross comparison of results. Thus the development of a standard protocol for human cytogenetic studies is needed, as is information on the background frequencies of chromosomal aberrations (CAs), particularly chromatid-type aberrations, and sister-chromatid exchanges (SCEs), their variability, and the sources of variability. This information will be useful in the design and interpretation of future cytogenetic studies of populations exposed to potential chromosome-damaging agents.

A project has been undertaken with two laboratories (Brookhaven National Laboratory, Dr. M. Bender; Oak Ridge National Laboratory, Dr. J. Preston): (1) to develop and standardize a protocol by which the frequencies of CAs and SCEs in lymphocytes can be accurately and reproducibly determined; and (2) to investigate the variation of the frequencies as affected by the protocol and, to the extent possible, by the circumstances of the individuals from whom blood samples are obtained.

A common protocol is now employed in both participating laboratories. Chromosomal aberration and sister-chromatid exchange data have been obtained on more than 250 subjects selected using a stratified, random sampling scheme. A questionnaire is used to obtain demographic data from all subjects. A computer file is used for storage and analysis of data. Blood samples have been obtained from the remaining 150 subjects in the study and cytogenetic analysis will be completed in the current year.

FY 1985 PROGRAM PLANS

During FY 1985, the findings of the study will be extended by expanding the study population to include older and younger age groups, increasing the number of non-white subjects and continuing to sample previously selected individuals through time. Results of the initial study will be published. (CONTACT PERSON: Dr. M. D. Shelby)

Mouse Erythrocyte Micronucleus Assay -- Micronuclei are cellular inclusions containing chromatin that are normally much smaller than the cell nucleus and result from the lagging of chromosome fragments or whole chromosomes during anaphase that subsequently are not incorporated into daughter nuclei. One cell type in which micronuclei are particularly easy to observe are the anucleate erythrocytes. Having their origin in broken chromosomes or disrupted mitoses, micronuclei have been utilized for several years as the basis for determining the genotoxicity of chemicals in intact rodents.

Recent studies have shown that the mouse micronucleus assay can be employed in chronic (>30 day), low dose exposures since micronucleated normocytes accumulate in the peripheral blood for approximately 40 days (the approximate lifetime of a circulating normocyte). These studies open the possibility of incorporating the mouse erythrocyte micronucleus assay into the NTP prechronic toxicity (and possibly chronic toxicity) studies as an indicator of induced cytogenetic damage.

A two-year project (USDA Western Regional Research Center, Dr. James MacGregor) to evaluate the utility of the mouse erythrocyte micronucleus test as an adjunct to the prechronic phase of chronic toxicity tests in rodents has been undertaken. The micronucleus test could provide a measure of the genotoxicity of the test agent by quantifying the frequency of peripheral erythrocytes bearing micronuclei that result from chromosomal breaks or disruption of the normal mitotic process. The test requires only a single drop of blood from each animal and therefore would have minimal impact on the prechronic toxicity test protocol or expense.

The objectives of this project are: (1) to determine if agents known to increase the frequency of micronucleated erythrocytes following acute, high-dose exposure also elevate the frequency of micronuclei in circulating erythrocytes during routine prechronic toxicity bioassays and, (2) to compare the relative sensitivity of the two dosage regimens and to determine the extent to which the frequency of micronuclei in the peripheral erythrocytes of prechronically-exposed mice correlated with the frequencies and types of tumors following long-term exposure.

In the first six months of this project, micronucleus data were obtained on four chemicals from slides of mouse blood provided by the NTP. For benzene, a dose-related increase in micronucleated erythrocytes was observed for both prechronic and chronic exposures. Positive results were also observed for ethylene dibromide and a marginal increase was seen in animals exposed to propylene oxide for two years. Animals exposed to ethylene oxide for two years exhibited no increase in micronuclei frequencies relative to the untreated controls.

FY 1985 PROGRAM PLANS

Additional efforts will be made to obtain blood smears from animals in 90-day toxicity studies. Micronucleus data on another 10-15 chemicals is anticipated in FY 1985. (CONTACT PERSON: Dr. M. D. Shelby)

- Gene Transposition Assays

Chemically Induced Transposition in *Drosophila* -- It has been demonstrated in *Drosophila* that a large proportion of apparently spontaneous mutations, including mutations recovered from natural populations, are the result of insertion of transposable elements. Transposition of these elements is very rare, however, under normal laboratory conditions. It is not known to what extent transposition is a cause of spontaneous mutation in mammals, nor is it known to what extent exposure to chemicals induces transposition. This contract (University of Kentucky, Dr. C. Osgood) is designed to answer the latter question in *Drosophila* and, if chemicals are found to induce transpositions, to design and develop an assay for chemically-induced transposition to be used as part of the Cellular and Genetic Toxicology Branch mutagen screening program.

Two steps are required to demonstrate that transpositions can be caused by chemicals. In the first step, individual flies carrying mutations known to result from transposons inserted into specific genes are treated with a chemical mutagen and the progeny of these individuals are examined for reversion of the mutations that were caused by the insertion. These progeny can also be examined for the appearance of new visible mutations at the same time. In the second step, DNA from the exceptional progeny (either the revertants or the progeny bearing new mutations) is examined on Southern blots to ask whether the reversions were caused by an excision of the transposable element that was originally present or whether the new mutations were due to an insertion of DNA into the gene that was mutated.

To date, a total of 58 ethyl methanesulfonate or ethyl nitrosourea-induced mutations at the RpII locus have been examined for changes in their restriction pattern on Southern blots; no insertions were found.

FISCAL 1985 PROGRAM PLANS

At this point it is not known whether chemicals induce transposition of mobile genetic elements. Given the almost total lack of knowledge in this area, it is not clear which chemical classes should be evaluated or which transposable elements should be used. Plans are to treat individuals carrying a number of different transposable elements inserted into known, cloned genes with a wide variety of chemicals and to look for both reversion and forward mutation. (CONTACT PERSON: Dr. J. Mason)

Mouse Endogenous Retroviral Long Terminal Repeat (LTR) Elements for Studying Gene Transposition in Environmental Carcinogenesis -- Retroviruses are well known to be involved in insertional mutagenesis and carcinogenesis. The structural similarity of retroviruses and transposable elements has opened the important question of whether endogenous retrovirus and related proviral elements are functionally transposable elements which may be potential targets of environmental genotoxic agents.

Through an Interagency Agreement with the Department of Energy at the Oak Ridge National Laboratory (Dr. W. K. Yang, Principal Investigator), analysis of the LTR of BALB/c endogenous xenotropic-like provirus recombinant DNA clones has revealed a mouse-specific middle repetitive sequence (called MboI, due to conserved MboI sites in this family) that is not present in any known infectious xeno- or ecotropic murine leukemia virus (MuLV). Endogenous MuLV LTRs with and without this repeated sequence are detected in the mouse genome. MuLV-related proviruses that do contain this MboI repeat appear to be a distinct class characterized by a glutamine tRNA primer binding site (for initiation of reverse transcription) rather than proline tRNA used by all known xeno- and ecotropic MuLVs. This class of provirus is more abundant than the infectious xeno- and ecotropic provirus. It is as yet uncertain whether an intracellular transposition mechanism is responsible for the multiple copies found dispersed in the mouse genome.

The vast majority of the MboI repeats are not associated with a typical MuLV LTR but are nevertheless contained within an LTR-like structure. These endogenous LTR-like structures have RNA transcription and polyadenylation consensus sequences characteristic of MuLV LTRs and are often flanked by short repeats characteristic of transposons and insertion elements. MuLV LTRs do not hybridize with these endogenous elements but distant homology can be detected by sequence analysis.

These LTR-like elements are likely to be very relevant to the retrovirus-transposon connection. Analysis of one particular molecular clone of

BALB/c DNA containing the MboI repeat has revealed a 5.5 Kbp structural component separated by two of the endogenous LTR-like elements and flanked by a 4 base pair direct repeat. This structural arrangement is equivalent to a provirus or a transposon, with the LTR-like elements serving as "Insertion Sequences." The 5.5 Kbp structure component, like the LTR, does not hybridize to MuLV, but computer analysis of sequence data does indicate distance homology with stretches of Moloney MuLV *gag* and *pol* sequences. As there is no known infectious activity, an extracellular transposition mechanism may be responsible for the dispersal of this element within the mouse genome.

FY 1985 PROGRAM PLANS

Characterization of these elements will be continued including analyis of their distribution within the genomes of various inbred mouse strains and various *Mus* species. Expression of LTR and MboI linked genes will be examined in various mouse cells and tissues and in heterologous cells by use of co-transfection assays with selectable markers. These experiments will provide the foundation of information necesary to develop assays for induced transposition of the MboI repeat and related gene elements. (CONTACT PERSON: Dr. R. W. Tennant)

- *Special Application*

Mutagens Formed From the Cooking of Foods -- The objectives of this interagency agreement with Lawrence Livermore National Laboratory have been to identify and characterize the mutagens produced in foods, primarily beef products, cooked under approximately normal household conditions, and determine their mechanism(s) of formation, assess the spectrum of genetic toxicity caused by these mutagens using *in vitro* and *in vivo* short-term tests, and devise strategies to limit or prevent mutagen formation.

Hamburger is fried under normal cooking conditions, extracted, and the extracts tested for mutagenicity using the *Salmonella* test. Extracts exhibiting the highest levels of mutagenicity are separated to isolate and identify the mutagenic components. Standard separation chemistry procedures are being used to isolate, purify, and identify individual mutagenic components of these extracts. Mutagens were present in beef, eggs, pork, ham, bacon, chicken, and some fish after being fried or broiled to a well-done state. Tofu, beans, cheese, and other fish, when cooked under similar conditions, produced low or negligible mutagenic activity. Studies with a model system based on beef which was boiled at 100°C indicate that all precursors for mutagen formation are water-soluble and of low molecular weight. The mutagens in these boiled beef extracts have been identified as IQ (2-amino-3-methylimidazo[4,5-d]quinoline), Trp-P-1 (3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole), and Trp-P-2 (3-amino-1-methyl-5H-pyrido[4,3-b]indole). Studies with radiolabelled tryptophan indicated that it is a precursor of Trp-P-1 and Trp-P-2 in this system; studies with radiolabelled creatine phosphate, a possible precursor of IQ, are planned.

Extraction of beef fried at 300°C shows the presence of approximately ten mutagenic fractions. The largest proportion of mutagenic activity is provided by MeIQx (2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline) (approximately 35% of total activity). The molecular weights and formulae of additional major mutagens have been determined. Several minor mutagens are present including IQ. Fried beef of high fat content (30%) contained twice as much IQ as the standard, lean (15% fat) ground beef.

In cultured Chinese hamster ovary (CHO) cells, Trp-P-2 was cytotoxic, mutagenic, and clastogenic. A DNA repair-deficient cell line (UV-5) was twice as sensitive to these effects as the parental line (AA8), IQ was cytotoxic in both strains (but a higher dose was needed than for Trp-P-2); mutations and SCE were produced, but chromosomal aberrations were not significantly increased. IQ did not induce mutagenic or clastogenic responses in AA8. The cytotoxicity and genotoxicity of these mutagens in CHO cells are inversely proportional to their response in Salmonella. Trp-P-2 was also more toxic than IQ in vivo. Both substances induced SCEs in mouse bone marrow. Chromosomal aberrations in mouse bone marrow were substantially increased with Trp-P-2; the response with IQ was negligible.

Salmonella and CHO cells were treated with radiolabelled Trp-P-2 and IQ. DNA was purified and the level of DNA adducts was measured. Trp-P-2 introduced approximately the same number of DNA adducts in Salmonella and CHO cells; and the induced mutations were also equivalent. IQ induced similar numbers of adducts in Salmonella as Trp-P-2, but induced mutations were lower. In CHO cells, however, much higher doses of IQ were required to induce the same levels of adducts as Trp-P-2. These experiments do not fully explain the unexpectedly low genetic toxicity of IQ in comparison with Trp-P-2 in CHO cells. However, at the concentrations reported to give similar numbers of DNA adducts, the two agents have similar mutagenic efficiencies in both assay systems.

Organic synthesis procedures have been developed for IQ and ^{3}H-IQ. The major effort in organic synthesis is an attempt to synthesize the unknown components of fried beef extracts. Mutagenic and metabolic studies will be performed on the newly-identified mutagens once the organic synthesis is developed and they can be prepared in sufficient quantities. Identification of mutagens formed in other protein-rich foods during cooking will be proceeding following characterization of the fried beef mutagens. (CONTACT PERSON: Dr. E. Zeiger)

- Heritable Effects - Mammalian Assays

Mouse Morphological Specific Locus Study -- Exposure of humans to mutagenic chemicals poses the potential risk of induced mutations in germ cells, the transmission of these mutations to subsequent generations, and an increase in frequencies of genetic diseases in the population. Determining the risk of such health effects must presently be approached through whole mammal assays because tests using lower organisms or mammalian cells in vitro do not address heritability of induced mutations, germ cell stage specificity, and special metabolic, physiological, and transport factors that might exist during the reproductive cell cycle. The morphological specific-locus method is, at present, the most practical and reliable means available in mammals for detecting induced heritable mutations.

The two basic objectives of this project (Oak Ridge National Laboratory, Dr. L. Russell) are to investigate chemically-induced mutation processes in mammalian germ cells using N-ethyl-N-nitrosourea (ENU) as a model mutagen, and to test environmentally significant chemicals for mouse germ cell mutagenicity.

The test employs two strains of mice to detect mutations at seven loci that affect visible characteristics (coat color, eye color, and ear shape). Treated males are mated to females that are homozygous for recessive mutant alleles at the seven loci. Offspring are expected to be heterozygous at the seven loci and appear as wild-type, having inherited dominant wild-type alleles from their fathers. Variant animals will appear if the male germ cell carries a mutant allele. Offspring are scored at weaning and variants are tested by breeding studies to determine the genetic basis for variation.

In the ENU studies, a dose-response curve for spermatogonia has been determined with doses of 50, 100, 150, 200 and 250 mg/kg. The curve is clearly non-linear. Split dose experiments using 10 doses of 10 mg/kg and 20 doses of 5 mg/kg suggest that an effective DNA repair system is operating on ENU-induced lesions in the spermatogonia. Experiments on germ cell stage sensitivity showed a high frequency of mutants among progeny conceived 30-40 days post-treatment. Studies of treated female mice have shown no evidence of induced mutations in mature oocytes.

Specific locus tests of 1,2-dibromo-3-chloropropane and hexamethylphosphoramide have been completed and are negative. The test of urethane is near completion with no indication of an effect. Ethylene dibromide and 6-mercaptopurine are on test.

FY 1985 PROGRAM PLANS

Experiments are planned to investigate ENU mutation induction in post-meiotic male germ cells, investigate the germ cell specificity of N-methyl-N-nitrosourea (MNU), conduct further studies of ENU in females, extend molecular dosimetry studies with ENU and MNU and initiate tests on two chemicals. (CONTACT PERSON: Dr. M. D. Shelby)

Mouse Biochemical Specific Locus Study -- The biochemical specific locus assay offers a second animal model with which to investigate the ability of chemicals to induce heritable mutations in mammalian germ cells. This assay has two particularly desirable features. First, the assay detects changes in specific enzymes or proteins and offers the opportunity to relate chemically-induced mutations to changes in enzyme structure and function, and ultimately to effects on health or fitness. Second, the potential availability of a large number of loci for analysis means that more information can be obtained from each F_1 animal than in the morphological specific locus test.

The objectives of this study (Research Triangle Institute, Dr. S. Lewis) are to investigate chemically-induced mutation processes in mouse germ cells by studying cell stage specificity in both sexes and establish a dose-response curve in spermatogonia using N-ethyl-N-nitrosourea (ENU) and ionizing radiation as model mutagens and to test a limited number of chemicals for germ cell mutagenicity.

Induced mutant frequencies are determined by treating one parent, usually the male, with a test chemical and then mating to untreated females to obtain progeny. Blood and kidney samples are taken from the progeny and tissue preparations of these samples are subjected to electrophoresis. After staining, the electrophoretic patterns of specific proteins are observed on the gels and altered mobility patterns or missing bands are noted. Breeding tests of the animals with altered proteins, along with additional electrophoretic analyses, are used to confirm the mutational basis of the variation.

In experiments to determine the ENU dose response in spermatogonia, the 250 mg/kg and 100 mg/kg doses have been completed and 200 mg/kg is near completion. A 50 mg/kg test is under way. Studies in ENU treated females have yielded two confirmed and one probable mutants in approximately 1500 progeny.

A mouse exhibiting a hemoglobin disorder analgous to β-thalassemia in humans was discovered last year during routine electrophoretic screening. Heritability has been confirmed and a stock of animals derived and made available to other laboratories for further research.

The germ cell mutagenicity of inhaled ethylene oxide (EO) was studied. In the initial test electrophoretic analysis of 30 loci in over 850 progeny conceived in the first week following exposure revealed no electrophoretic variants, but of three morphological variants detected, one has proven to be heritable and one was associated with a translocation. The second ethylene oxide study produced seven electrophoretic morphological variants among 1200 offspring.

FY 1985 PROGRAM PLANS

The 50 mg/kg ENU spermatogonia experiment and the ethylene dibromide test will be completed. The responsiveness of the system to ionizing radiation will be characterized. (CONTACT PERSON: Dr. M. D. Shelby)

Mouse Heritable Translocation Testing -- Heritable translocations resulting from the exchange of segments between non-homologous chromosomes are known to result in serious human diseases such as Down's and cri du chat syndromes. The fact that serious genetic disease can result from heritable translocations, together with the fact that radiation and a number of chemicals are known to induce such heritable damage in mammalian germ cells, demonstrates the need for testing chemicals for the ability to induce heritable translocations.

This study (Oak Ridge National Laboratory, Dr. W. Generoso) will gather additional information on the heritable genetic effects of chemicals being tested in the morphological specific locus assay.

Heritable translocations are detected following treatment of male mice with test chemicals, mating with untreated females, and then testing F_1 males for fertility. Partially or completely sterile F_1 males are confirmed as translocation carriers by additional matings and cytogenetic analyses. Dominant lethal studies are conducted prior to the heritable translocation tests to obtain preliminary information on the potential germ cell mutagenicity of the test chemical, appropriate dose levels, and cell stage sensitivity.

A study with inhaled ethylene oxide (EO) revealed a clear dose-response effect for both dominant lethals and heritable translocations. Extensive studies with 1,2-dibromo-3-chloropropane (DBCP) were conducted including multiple dosing and both intraperitoneal and subcutaneous injections. No effects on fertility or dominant lethal frequency were observed.

Hexamethylphosphoramide and urethane have given uniformly negative dominant lethal results. Tetrahydrocannabinol has been negative in both dominant lethal and heritable translocation tests. Ethanol administered orally to females shortly after mating has been shown to increase the frequency of late fetal deaths.

FY 1985 PROGRAM PLANS

Results of completed tests will be published, and three additional compounds will be selected and tested. (CONTACT PERSON: Dr. M. D. Shelby)

- Collaborative Activities

Collaborative Study on Short-Term Tests -- The NTP continues to be represented on the International Program on Chemical Safety (IPCS) Ad Hoc Working Group on the Application of Short-Term Tests to Predict Mutagenic and Carcinogenic Potential, and participates in the *in vitro* and *in vivo* phases of the project.

The objective of the *in vitro* phase of the study is to evaluate a range of eukaryotic *in vitro* tests which, in a battery testing approach, might complement bacterial gene mutation assays by reliably detecting chemical carcinogens that are not readily detected with bacterial systems. Eight selected carcinogens were tested, (hexamethylphosphoramide, safrole, ortho-toluidine, benzene, acrylonitrile, di(2-ethylhexyl) phthalate, phenobarbital, and diethylstilbestrol), as were two chemicals (benzoin and caprolactam) for which there is good evidence of noncarcinogenicity. Assays complementary to bacterial tests cannot be selected strictly on the basis of a ten-chemical study, and other major sources of data such as the International Program for the Evaluation of Short-Term Tests for Carcinogens (IPESTTC) and the EPA Gene-Tox Program will be used to assess the assay system under study.

In the second phase of this IPCS project, a wide range of short-term *in vivo* genotoxic assays and endpoints will be employed to assess the activity of two pairs of carcinogens/putative noncarcinogens (benzo(a)pyrene/pyrene and 2-acetylaminofluorene/4-acetylaminofluorene). In each pair, both members have been found to give positive results with *in vitro* assays while limited results with short-term *in vivo* assays have shown the carcinogen positive and the putative noncarcinogen negative. This phase of the study is intended to elucidate the mutagenic and potential carcinogenic activity of these four chemicals in intact animals.

Sixty investigators participated in the *in vitro* phase of the study. Testing was completed and a meeting of investigators was held in 1983. The complete results of the study have been submitted for publication as a book.

In the *in vivo* study, more than 50 investigators are currently conducting tests on the four test chemicals.

FY 1985 PROGRAM PLANS

A meeting of all participants in the in vivo phase will be held in February 1985 to review and discuss results among similar assays and to review test result profiles for each of the four chemicals. Results of the study will be published. (CONTACT PERSON: Dr. M. D. Shelby)

INTRAMURAL PROGRAM

FY 1984 ACCOMPLISHMENTS AND FY 1985 PROGRAM PLANS

Salmonella Mutagenesis Research -- Research with Salmonella typhimurium tester strains can be divided into: (1) studies on the Salmonella strains and protocols in order to increase understanding of the test and improve the sensitivity and efficiency of the protocols currently in use, and (2) use of the Salmonella test as a tool to study the metabolism of mutagenic chemicals.

Studies designed to improve understanding of the test include: (1) kinetics of generation and appearance of spontaneous and induced mutant colonies in the plate test; (2) factors affecting the mutation responses; (3) identification of sources of variability or error in the test; (4) enhancement of the sensitivity of the protocols and improvement of the efficiency of currently used protocols; and (5) characterization of the factors needed to define a positive mutagenic response. Examples of these studies are the identification of chemicals which interfere with the appearance of histidine revertant colonies in the plate test in the absence of toxicity as normally measured in the test; the characterization of two new Salmonella tester strains, TA97 and TA102; studies with sodium bisulfite which have shown that the Salmonella strains can survive and be mutagenized under acidic conditions (pH 5); a determination of the stability of working solutions of various chemical mutagens used as positive controls; and studies that showed that, contrary to expectations, DNA repair-deficient Salmonella strains are mutagenized less than wild-type cells at low doses of mutagen (ethyl methanesulfonate), whereas high doses are more mutagenic to repair-deficient cells. This effect is being studied further.

Projects using Salmonella to study the metabolism of mutagens include those which examine different enzyme systems, such as prostaglandin endoperoxide synthetase (PES), and those which investigate cytochrome-based metabolism in organs other than liver.

Studies with different Salmonella strains to ascertain the structure(s) of the PES-generated mutagenic metabolic intermediates(s) of 2-aminofluorene showed that the PES system is not oxidizing 2-aminofluorene to the proximate mutagen 2-nitrofluorene, but rather the pattern of metabolism appears to be similar to that seen with liver homogenates.

The mutagenicity of benzo(a)pyrene (BaP) and benzidine (BZ) in Salmonella strain TA98 was examined in the presence of 9000xg (S-9) supernatants of liver, prostate, and testes from untreated rats and rats pretreated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). BaP was mutagenic in the presence of liver, prostate, and testes S-9 fractions from TCDD-treated rats; little or no mutagenicity was seen under the same conditions with S-9s from untreated rats. BZ was not mutagenic in the presence of testes S-9 but it was mutagenic

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with TCDD-induced prostate S-9 and with both noninduced and TCDD-induced liver S-9.

Studies are under way to investigate the organ-specific metabolism, in vitro and in vivo, of a number of mutagens which are organ-specific carcinogens. (CONTACT PERSON: Dr. E. Zeiger)

Molecular Mechanisms of Recombination and DNA Repair in Yeast --Meiosis is the developmental stage which occurs in nearly all eukaryotes resulting in the formation of gametes. Although there is considerable information on the heightened genetic and morphological changes that take place during this process, little is known about DNA metabolic events, DNA repair, or mechanisms of mutation. Yeast is the only organism with which it is possible to study simultaneously the molecular and genetic events, the role of DNA repair, and the enzymology and the genetic control of meiosis. The purpose of this research program is threefold: (1) to further characterize the mechanisms of repair in yeast; (2) to determine the importance of chromosomal structure on the induction and repair of DNA damage, particularly in centromeric regions of chromosomes; and (3) to determine the role of DNA repair mechanisms in the process of normal meiosis and in dealing with external insults during meiosis.

The genetic consequences of a DNA damaging agent depends on the distribution of damage in the chromosome. Structural constraints caused by folding, superhelicity, and chromosomal proteins might be expected to affect the susceptibility to DNA damage. Because of the severe genetic consequences anticipated from damage in the centromeric region of a chromosome and the unique structure of centromeres, investigations have begun on the induction and repair of DNA damage in this region, using DNA probes specific for centromeres. It appears that centromeric DNA in excision-defective strains may be particularly resistant to UV-induced damage when compared to the rest of the chromosome or to purified DNA.

Using various repair and meiotic mutants of the yeast Saccharomyces cerevisiae, the mitotically defined excision, postreplication, and double-strand break repair pathways are being examined in meiosis. There is only one excision-repair pathway available to cells undergoing meiosis; however, in its absence cells lacking this pathway can still tolerate a considerable amount of damage due to an ability to replicate DNA past the damage. The unrepaired damage can alter meiotic events substantially as evidenced by the several-fold suppression of meiotic recombination and the absence of molecular exchanges.

While the excision repair pathway is not required for normal meiosis, the double-strand break repair pathway is essential. In mutants lacking the RAD52 and RAD50 gene products, cells die as they enter meiosis. The RAD52 pathway is essential in mutagenesis by ethyl methanesulfonate and methylmethane sulfonate and in repairing ionizing radiation-induced damage. NTP investigators found that the enzyme which is lacking in rad52 mutants is an alkaline deoxyribonuclease and, based on physical studies of meiotic DNA, it appears to process intermediates in molecular recombination. The further characterization of this enzyme which has been purified to near-homogeneity will contribute appreciably to an understanding of recombination repair and mutagenesis in yeast and other organisms.

Single-strand interruption intermediates accumulate during meiosis in rad52 mutants and may represent sites of initiation for recombination based on genetic evidence and their distribution, as modelled mathematically. This possibility is being examined by isolating and specifically examining DNA containing the interruptions for DNA sequence and nature of interruptions. Using genetic techniques, it has been possible to order the steps leading to the accumulation of interruptions.

As part of ongoing studies to develop a genetic and biochemical profile, the Branch is examining DNA metabolic enzymes in specially developed strains that exhibit high levels of meiotic synchrony. The DNA polymerases I and II, the Mg^{++} dependent nucleases, and the RAD52-controlled nuclease increase at about the time of meiotic DNA synthesis, implying a coordinated increase in these enzymes with the onset of meiosis. While the polymerases increase by about two-fold there is a greater than 10-fold increase in nucleases, suggesting they may have an important role in recombination. Initial results suggest a role for methylation of DNA during meiosis, possibly as a regulatory mechanism in development. (CONTACT PERSON: Dr. M. A. Resnick)

Molecular Genetics of Meiosis and Mutagenesis in Yeast -- Eukaryotes have developed a universal and highly structured mechanism to insure the faithful transmission of genetic information to the next generation. This fundamental mechanism, meiosis, is usually accompanied by the differentiation of diploid germ line cells to produce haploid gametes. Both meiosis-specific (germ line) functions and general somatic functions (recruited from the mitotic cell cycle) are combined to effect the unique events of meiosis. As the carriers of genetic information, an understanding of the behavior of chromosomes and their associated DNA metabolism during these unique meiotic events is critical to an evaluation of the genetic consequences of environmental challenge to germ line cells.

The strategy adopted to investigate these problems is to focus on the cellular functions which are required for the unique metabolism of chromosomes during meiosis in the yeast *Saccharomyces cerevisiae*. A three-step experimental approach is employed: (1) identify meiosis-essential functions by mutation; (2) isolate the meiotic functions by gene cloning; and (3) analyze the function of the cloned gene by *in vitro* mutagenesis, gene replacement in yeast, and identification of the gene product in *E. coli* by recombinant DNA procedures.

Current efforts have focused on the yeast SPO11 gene which is required for recombination and proper chromosome segregation during meiosis. To analyze its function and regulation, the SPO11 gene has been physically isolated by cloning. This represents the first isolation and identification of a gene product essential for meiosis. The structure and function of the cloned gene is being analyzed by restriction enzyme mapping, subcloning, and by insertional mutagenesis using the bacterial transposon, Tn5.

The selective system developed to isolate the SPO11 gene is general and may be used to isolate any meiosis-specific gene of yeast for which a mutant is available. The gene products which mediate meiotic DNA metabolism in germ line cells are at present unidentified. The purified SPO11 will be used as a probe of the mechanism and regulation of meiosis in yeast. As a complement to the SPO11 studies, a second meiosis-specific gene, pac1, is also being examined. In

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addition, strain construction is in progress to construct an improved genetic system which, when combined with the transposon-mediated insertional mutagenesis methods currently being used on the *SPO11* gene, will allow *in vitro* mutagenesis and *in vivo* genetic analysis to be combined for a detailed molecular genetic analysis of meiosis-specific genes in yeast.

A second major focus of the research program is the examination of the mechanisms whereby genetic information is transmitted to progeny somatic cells with fidelity, how mutagenesis occurs, and what mechanisms the cell employs to avoid mutation. Using a combination of classical genetic and recombinant DNA techniques, a model system is being constructed to examine the molecular basis of mutagenesis in *Saccharomyces cerevisiae*. This system will use a cloned suppressor tRNA gene as a mutagenesis target, the *SUP4-O* gene. Loss of target suppressor function following exposure of the test system to mutagenic challenge will be assessed by positive genetic selection. A spectrum of the molecular changes occurring in the target DNA sequence as a consequence of the mutagenic challenge will then be determined.

At present, little specific information is available about the molecular nature of mutation in eukaryotes. Development of a test system in yeast which would provide DNA sequence information for particular mutagenesis events would help fill this gap in our knowledge. In addition to providing basic information about the nature and mechanism of mutation in a eukaryote, this test system could also be used to evaluate the mutagenic effects of a chemical or physical agent, both in quantitative (dose response) and qualitative (mutational spectrum) terms. By comparing the mutagenic spectrum of the wild type test system with those of the specific repair pathway deficient test systems, the role of each pathway in mutation avoidance and the metabolism of potentially mutagenic DNA damage will be examined. This fundamental information will allow a more accurate determination of how a eukaryote responds to mutagenic challenge by specific environmental agents. (CONTACT PERSON: Dr. C. N. Giroux)

DNA Repair and Mutagenesis in Drosophila -- Mutation rates are under genetic control. In bacteria and yeast, for example, induced mutation frequencies can be altered by blocking one or another DNA repair pathway. This project is designed to determine the relationship between DNA repair and mutagenesis in *Drosophila melanogaster*.

The general approach is an in-depth genetic analysis of mutants that are defective in DNA repair to ascertain, for example, their (1) effects on spontaneous and induced mutation frequencies, including chromosome aberrations; (2) pleiotropic effects on recombination, meiotic chromosome segregation, and transposition of mobile genetic elements; and (3) genic organization. All of the experiments employ standard genetic manipulations utilizing well-characterized mutants and chromosomal aberrations.

One mutator being examined is unable to repair X-ray-induced chromosome breaks in the normal way. In its presence broken chromosomes are recovered which do not appear to be capped by a previously existing telomere; that is, terminal deletions are recovered that are not associated with chromosome rearrangements such as translocations. The mutator is recessive and maps near the end of the left arm of chromosome III. It is active primarily in later stages of oocyte development, but not during spermiogenesis. The mutator shows a slight decrease in the frequency of meiotic recombination but has little or no effect on nondisjunction. It does, however, increase the frequency of X-chromosome loss. The breaks that are recoverable appear to be randomly distributed; they can be on any of the four chromosomes, they can be recovered near the tip, in the centric heterochromatin, or in the middle of the X chromosome.

The telomeres of a number of terminally-deleted chromosomes are being cloned in order to characterize them and develop a consensus sequence for functional telomeres in *Drosophila*.

Transposable elements in *Drosophila* cause a wide range of genetic effects including mutation, mitotic recombination, chromosome aberrations and sterility. The control of transposition is poorly understood in any system. We have asked whether cellular functions are important in the control of transposition by combining mutants defective in DNA repair and recombination with transposable elements. If such functions are important for transposition, the transposon-induced frequencies of mutation and recombination should be altered; they are not. Mutants at four different loci had no effect on either mutation or recombination frequencies. Mutants at the *mei-41* locus, however, drastically reduced the recovery of transposon-bearing chromosomes in the following generation. The mechanism for this is unknown, but loss of transposon-bearing chromosomes is correlated with dominant lethality.

A genetic fine structure map of the DNA repair defective mutant *mei-41* region has been constructed using several independently isolated alleles. This map confirms the large size of *mei-41* found during mutational analysis. The *mei-41* locus is estimated to cover approximately 300 kilobase pairs of DNA. To confirm that the *mei-41* locus is large at the DNA level and to gain some insight into the structure and control of a large locus, new *mei-41* mutations are being made using transposons and the locus will be cloned using the transposon tagging method. (CONTACT PERSON: Dr. J. Mason)

Mammalian Cell Molecular Genetics -- The cellular homologue (c-onc) of oncogenes first identified as components of acutely transforming retroviruses have been shown to be expressed by the adjacent integration of a non-oncogene containing retrovirus. This promoter insertion model of oncogenesis and the altered expression of cellular oncogenes has been extended to non-viral neoplasms as well. Chromosomal translocations, gene amplification and mutation of c-oncs have all been implicated in various natural and experimental neoplasms. We have been studying endogenous ecotropic provirus rearrangements as a model for oncogenesis by transposition and promoter insertion, and have detected somatically reintegrated copies for the endogenous ecotropic provirus in greater than 85% of the spontaneous reticulum cell sarcomas of the RFM/Un mouse strain and also in some radiation induced myeloid leukemias. The goal has been to identify common integration domains in independent primary neoplasms. Such domains are likely to contain genes important for the neoplastic phenotype. To this end, we have molecularly cloned and analyzed two unique provirus integration sites from spleen DNA of an animal with radiation induced myeloid leukemia. The flanking cellular sequences have been used as probes and preliminary results suggest that some independent neoplasms have rearrangements involving these sequences.

Continuation of this research will involve the identification of the chromosomal location of these two cloned somatically acquired proviruses and linkage with any known oncogene. Proviruses will be cloned from other tumor phenotypes, principally the reticulum cell sarcomas, and the flanking regions compared with those from myeloid leukemia. It is anticipated that distinct domains will be involved in those two neoplasms. In addition, chemically induced neoplasms are being examined by similar techniques. A small number of 5-azacytidine induced tumors do show rearrangements of the endogenous ecotropic provirus and these will be examined further. We have also cloned many nonecotropic provirus related sequences, including solitary LTRs and are analyzing the structure and function of these elements in normal and neoplastic cells. Studies are being conducted in collaboration with Dr. W. K. Yang, Biology Division, Oak Ridge National Laboratory. (CONTACT PERSONS: Dr. L. R. Boone and Dr. R. W. Tennant)

TABLE 1

CHEMICAL TEST RESULTS FOR MUTAGENICITY IN SALMONELLA ASSAYS IN FY 1984

SEQ. NO.	CHEMICAL	RESULTS * **	CAS NO.
1	1-ACETYL-2-PHENYL HYDRAZIDE	+	114-83-0
2	ACRYLAMIDE	-	79-06-1
3	AFLATOXIN EXTRACT AA 34-1	+	EMTDP-1
4	AFLATOXIN EXTRACT AA 34-2	+	EMTDP-2
5	AFLATOXIN EXTRACT AA 34-4	+	EMTDP-3
6	AFLATOXIN EXTRACT AA 34-5	+	EMTDP-4
7	AFLATOXIN EXTRACT AA 34-6	+	EMTDP-5
8	AFLATOXIN EXTRACT AA 34-7	+	EMTDP-6
9	AFLATOXIN EXTRACT AA 34-8	+	EMTDP-7
10	AFLATOXIN EXTRACT AA 34-9	+	EMTDP-9
11	ALLYL ACRYLATE	-	999-55-3
12	P-AMINO ACETANILIDE	+	122-80-5
13	M-AMINOACETANILIDE	+	102-28-3
14	4-AMINO-2-NITROPHENOL	+	119-34-6
15	4-AMINOPHENOL	-	123-30-8
16	AZINPHOSMETHYL	+W	86-50-0
17	BENZAMIDE	-	55-21-0
18	BENZONITRILE	-	100-47-0
19	BENZO(F)-QUINOLINE	+	85-02-9
20	BENZOYL PEROXIDE	-	94-36-0
21	BENZYL CHLORIDE	+W	100-44-7
22	BENZYLTRIMETHYL AMMONIUM CHLORIDE	-	56-93-9
23	2-BIPHENYLAMINE	+,+	90-41-5
24	2,4-BIS(P-AMINOBENZYL) ANILINE	+	25834-80-4
25	1,3-BIS(2-BENZOTHIAZOLYLMERCAPTOMETHYL) UREA	+	64216-20-2
26	2-BROMO-1-ETHANOL	+	540-51-2
27	2-BROMOETHYL ACRYLATE	+	4823-47-6
28	BETA-BROMO-BETA-NITROSTYRENE	+	7166-19-0
29	MONO-SEC-BUTANOLAMINE	-	13552-21-1
30	BUTYLTIN-TRIS(ISOOCTYLMERCAPTOACETATE)	-	25852-70-4
31	CALCIUM CHROMATE	+	13765-19-0
32	CASTOR OIL	-	8001-79-4
33	CHLORAL	+	75-87-6
34	CHLORINATED TRISODIUM PHOSPHATE	+W	56802-99-4
35	P-CHLOROANILINE	+	106-47-8
36	M-CHLOROANILINE	?	108-42-9
37	4-CHLORO-O-PHENYLENEDIAMINE	+	95-83-0
38	3-CHLORO-1,2-PROPANEDIOL	+	96-24-2
39	C.I. ACID ORANGE 10	-	1936-15-8
40	C.I. ACID ORANGE 3	+	6373-74-6
41	C.I. DISPERSE BLUE 1	+	2475-45-8
42	C.I. SOLVENT YELLOW 14	+	842-07-9

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE
** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

TABLE 1

CHEMICAL TEST RESULTS FOR MUTAGENICITY IN SALMONELLA ASSAYS IN FY 1984

SEQ. NO.	CHEMICAL	RESULTS * **	CAS NO.
43	CINNAMYL ANTHRANILATE	-	87-29-6
44	COCONUT DIETHANOLAMIDE	-	68603-42-9
45	CODEINE	-	76-57-3
46	CODEINE PHOSPHATE	-	52-28-8
47	CYCLOHEXYL ANTHRANILATE	-	7779-16-0
48	DACARBAZINE	+	4342-03-4
49	DAMMAR	-	9000-16-2
50	D & C RED 9	+	5160-02-1
51	DIAMINOMALEONITRILE	-	1187-42-4
52	DIAZINON	-	333-41-5
53	DIBENZOOXATHIANE	-	262-20-4
54	1,2-DIBROMO-3-CHLOROPROPANE	+	96-12-8
55	DI-TERT-BUTYL PEROXIDE	-	110-05-4
56	DIBUTYLTIN-BIS(LAURYLMERCAPTIDE)	-	1185-81-5
57	DIBUTYLTIN DILAURATE	-	77-58-7
58	3,4-DICHLOROANILINE	-	95-76-1
59	1,2-DICHLOROETHANE	+	107-06-2
60	2,3-DICHLORO-1-PROPANOL	+	616-23-9
61	DICUMYL PEROXIDE	-	80-43-3
62	DICYCLOHEXYLAMINE NITRITE	+	3129-91-7
63	N,N'-DICYCLOHEXYLTHIOUREA	-	1212-29-9
64	DIETHYLBUTYLAMINE	-	4444-68-2
65	2,4-DIFLUOROANILINE	+	367-25-9
66	DIHEXYLAMINE	-	143-16-8
67	2,6-DIISOCYANATOTOLUENE	+	91-08-7
68	3-DIMETHYLAMINOPHENOL	+	99-07-0
69	2,5-DIMETHYL-2,5-BIS(TERT-BUTYLPEROXY)HEXANE	-	78-63-7
70	1,1-DIMETHYL-1-(2-HYDROXPROPYLAMINE)METHACRYLIMIDE	-	17341-40-1
71	4-(2,4-DINITROANILINO)PHENOL	+	119-15-3
72	DI(N-OCTYL)TIN-S,S'-BIS(ISOOCTYLMERCAPTOACETATE)	+	26401-97-8
73	DI(N-OCTYL)TIN MALEATE	-	16091-18-2
74	DIPHENYLUREA	+W	102-07-8
75	DIRECT VIOLET 32	-	6428-94-0
76	EPHEDRINE SULFATE	-	134-72-5
77	EPINEPHRINE	?	51-43-4
78	ETHACRYNIC ACID	-	58-54-8
79	ETHIONAMIDE	-	536-33-4
80	ETHYL ACRYLATE	-	140-88-5
81	3-ETHYLAMINO-4-METHYLPHENOL	+	120-37-6
82	3-ETHYLAMINOPHENOL	+	621-31-8
83	ETHYLBENZENE	-	100-41-4

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE

** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

TABLE 1

CHEMICAL TEST RESULTS FOR MUTAGENICITY IN SALMONELLA ASSAYS IN FY 1984

SEQ. NO.	CHEMICAL	RESULTS * **	CAS NO.
84	ETHYLENEDIAMINE	+	107-15-3
85	ETHYLENEDIAMINE TETRAACETIC ACID (EDTA)	-	150-38-9
86	2-ETHYLHEXANOIC ACID	-	149-57-5
87	2-ETHYLHEXYL ACRYLATE	-	103-11-7
88	N-ETHYLMORPHOLINE	+W	100-74-3
89	N-ETHYL-N-PHENYL BENZYLAMINE	-	92-59-1
90	FORMULATED FENAMINOSULF	+	140-56-7
91	FLUOMETURON	-	2164-17-2
92	FORMALDEHYDE	+	50-00-0
93	FORMANILIDE	-	103-70-8
94	FUMARIC ACID	-	110-17-8
95	BETA-2-FURYLACROLEIN	-	623-30-3
96	GLYCIDOL	+	556-52-5
97	HC BLUE 2	+	33229-34-4
98	HC RED 3	+	2871-01-4
99	HEXAFLUOROACETONE SESQUIHYDRATE	-	13098-39-0
100	1,6-HEXAMETHYLENE DIACRYLATE	-	13048-33-4
101	HYDROXYACETONITRILE	-	107-16-4
102	N-HYDROXYBENZAMIDE	+	495-18-1
103	ALPHA-HYDROXYBENZENEACETONITRILE	-	532-28-5
104	2-HYDROXY-2-METHYLPROPANENITRILE	-	75-86-5
105	3-HYDROXY-N-PHENYLANILINE	-	101-18-8
106	2-HYDROXYPROPANENITRILE	+W	78-97-7
107	IODINATED GLYCEROL	+	5634-39-9
108	N-ISOPROPYLANILINE	?	768-52-5
109	ISOPROPYL PHENYL DIPHENYL PHOSPHATE (IPDP MIXED ISOMERS)	-	28108-99-8
110	LAURIC ACID DIETHANOLAMINE CONDENSATE	-	120-40-1
111	MALONIC DINITRILE	-	109-77-3
112	P-MENTHANE	-	99-82-1
113	PARA-MENTHANE HYDROPEROXIDE	+	80-47-7
114	DL-MENTHOL	-	15356-70-4
115	2-MERCAPTOBENZIMIDAZOLE	-	583-39-1
116	METASYSTOX R	+	301-12-2
117	METHACRYLONITRILE	-	126-98-7
118	METHOXYCHLOR	-	72-43-5
119	4-METHOXY-3-NITRO-N-PHENYLBENZAMIDE	+	97-32-5
120	METHYL ACRYLATE	-	96-33-3
121	2-METHYLBENZAMIDE	-	527-85-5
122	2-METHYL-3-BUTENENITRILE	+W	16529-56-9
123	2-METHYL-2-BUTENENITRILE	-	4403-61-6
124	METHYL CARBAMATE	-	598-55-0
125	METHYLDOPA	-	555-30-6

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE

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CHEMICAL TEST RESULTS FOR MUTAGENICITY IN SALMONELLA ASSAYS IN FY 1984

SEQ. NO.	CHEMICAL	RESULTS * **	CAS NO.
126	N,N'-METHYLENEBISACRYLAMIDE	+	110-26-9
127	4,4'-METHYLENEBIS(2-CHLOROANILINE)	+,+,+	101-14-4
128	METHYL METHACRYLATE	-	80-62-6
129	N-METHYLOLACRYLAMIDE	-	924-42-5
130	MUSK KETONE	-	81-14-1
131	NALIDIXIC ACID	-	389-08-2
132	M-NITROACETOPHENONE	+	121-89-1
133	P-NITROANILINE	+	100-01-6
134	O-NITROANILINE	-	88-74-4
135	O-NITROANISOLE	+	91-23-6
136	M-NITROBENZAMIDE	+	645-09-0
137	P-NITROBENZAMIDE	+W	619-80-7
138	O-NITROBENZAMIDE	+	610-15-1
139	M-NITROBENZOYL CHLORIDE	+	121-90-4
140	2-NITRO-1,1'-BIPHENYL	-	86-00-0
141	P-NITROPHENETHYL ALCOHOL	+	100-27-6
142	M-NITROPHENOL	+	554-84-7
143	(O-NITROPHENYL)ACETONITRILE	+	610-66-2
144	4-NITROPHTHALIC ANHYDRIDE	+	5466-84-2
145	4-NITROPHTHALIMIDE	+	89-40-7
146	N-NITROSODIETHANOLAMINE	+	1116-54-7
147	N-NITROSODIMETHYLAMINE	+	62-75-9
148	N-NITROSOPIPERIDINE	+	100-75-4
149	OCHRATOXIN A	-	303-47-9
150	OCTACHLORODIBENZODIOXIN	-	3268-87-9
151	N-OCTYL METHACRYLATE	-	2157-01-9
152	OXETHAZAINE	-	126-27-2
153	4,4'-OXYDIANILINE	+	101-80-4
154	PERACETIC ACID	-	79-21-0
155	PHENAMIPHOS	-	22224-92-6
156	PHENETHYL ANTHRANILATE	-	133-18-6
157	O-PHENETIDINE	+W	94-70-2
158	PHENYLACETONITRILE	-	140-29-4
159	N-PHENYLBENZENAMINE	-	122-39-4
160	2-PHENYL-2-ETHYLMALONDIAMIDE	+W	80147-40-6
161	N-PHENYL-2-NAPHTHYLAMINE	-	135-88-6
162	PROMETHAZINE HYDROCHLORIDE	-	58-33-3
163	PROPANTHELINE BROMIDE	-	50-34-0
164	PROPIONITRILE	-	107-12-0
165	1,3-PROPYLENE OXIDE	+	503-30-0
166	3-PROPYLIDENEPHTHALIDE	+	17369-59-4

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE
** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

TABLE 1

CHEMICAL TEST RESULTS FOR MUTAGENICITY IN SALMONELLA ASSAYS IN FY 1984

SEQ. NO.	CHEMICAL	RESULTS * **	CAS NO.
167	QUATERNARY AMMONIUM COMPOUNDS, BENZYL-C8-18-ALKYLDIMETHYL, CHLORIDES	-	63449-41-2
168	QUINIDINE	?, -	56-54-2
169	RESERPINE	-	50-55-5
170	RIDDELLINE	+	23246-96-0
171	SALICYLAZOSULFAPYRIDINE	-	599-79-1
172	SENECIPHYLLINE	+	480-81-9
173	SODIUM ARSENILATE	-	127-85-5
174	MONOSODIUM METHANE ARSENATE	-	2163-80-6
175	SUCCINIC ANHYDRIDE	-	108-30-5
176	SUCCINONITRILE	-	110-61-2
177	TETRACHLORVINPHOS	-	961-11-5
178	TETRAETHYLDITHIOPYROPHOSPHATE	+	3689-24-5
179	3, 3', 5, 5'-TETRAMETHYLBENZIDINE	-	54827-17-7
180	THEOPHYLLINE	-	58-55-9
181	2, 2'-THIOBIS(4, 6-DICHLOROPHENOL)	-	97-18-7
182	4, 4'-THIODIANILINE	+	139-65-1
183	TITANIUM DIOXIDE	-	13463-67-7
184	TOLUENE ETHYLSULFONAMIDE	+W	8047-99-2
185	O-TOLUNITRILE	-	529-19-1
186	P-TOLUNITRILE	-	104-85-8
187	4, 4, 4-TRICHLORO-1, 2-EPOXYBUTANE	+	3083-25-8
188	1, 1, 2-TRICHLOROETHANE	-	79-00-5
189	TRIPHENYLAMINE	?	603-34-9
190	TRIS(1, 3-DICHLORO-2-PROPYL) PHOSPHATE	+, +	13674-87-8
191	UROTROPINE	?	100-97-0
192	VALERONITRILE	?	110-59-8
193	2, 4-XYLIDINE	+	95-68-1
194	2, 5-XYLIDINE	+	95-78-3
195	3, 4-XYLIDINE	+	95-64-7
196	3, 5-XYLIDINE	+	108-69-0

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE
** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
1	2-ACETYLAMINO-4-METHYLPHENOL	6375-17-3
2	N-ACETYL-M-AMINOPHENOL	621-42-1
3	ACETYLSALICYLIC ACID	50-78-2
4	N-ACETYL-M-TOLUIDINE	537-92-8
5	N-ACETYL-P-TOLUIDINE	103-89-9
6	ADIPONITRILE	111-69-3
7	AGARITINE	2757-90-6
8	ALDICARB	116-06-3
9	ALLOXAN	50-71-5
10	ALLOXAN MONOHYDRATE	3237-50-1
11	ALLYLTHIOUREA	109-57-9
12	AMILORIDE HCL	2016-88-8
13	2-AMINOACETANILIDE	555-48-6
14	5-(4-AMINOBENZAMIDO)-2,3-CRESOTIC ACID	6265-15-2
15	2-AMINOBENZENESULFONIC ACID	88-21-1
16	3-AMINOBENZENESULFONIC ACID	121-47-1
17	4-AMINOBENZENESULFONIC ACID	121-57-3
18	2-AMINOBENZIMIDAZOLE	934-32-7
19	2-AMINO-4-CHLORO-6-NITROPHENOL	6358-08-3
20	2-AMINO-6-CHLORO-4-NITROPHENOL	6358-09-4
21	2-AMINO-4-CHLOROPHENOL	95-85-2
22	6-AMINO-4-CHLORO-1-PHENOL-2-SULFONIC ACID	88-23-3
23	2-AMINO-4,6-DICHLOROPHENOL	527-62-8
24	2-AMINO-4,6-DINITROPHENOL	96-91-3
25	4-AMINO-4'-HYDROXY-3-METHYL-DIPHENYLAMINE	6219-89-2
26	1-AMINO-2-METHYLANTHRAQUINONE	82-28-0
27	2-AMINO-4-METHYLPHENOL	95-84-1
28	3-AMINO-6-METHYLPHENOL	2835-95-2
29	3-AMINO-4-METHYLPHENOL	2836-00-2
30	2-AMINO-4-(METHYLSULFONYL)PHENOL	98-30-6
31	2-AMINO-5-NITRO-4-METHYLPHENOL	6265-06-1
32	2-AMINO-3-NITRO-4-METHYLPHENOL	6265-05-0
33	6-AMINO-4-NITRO-1-PHENOL-2-SULFONIC ACID	96-67-3
34	2-AMINO-6-NITRO-1-PHENOL-4-SULFONIC ACID	96-93-5
35	2-AMINO-1-PHENOL-4-SULFONIC ACID	98-37-3
36	5-AMINO-3-SULFOSALICYLIC ACID	6201-87-2
37	3-AMINO-5-SULFOSALICYLIC ACID	6201-86-1
38	3-AMINOTRIAZOLE	61-82-5
39	2-AMINO-3,4,6-TRICHLOROPHENOL	6358-15-2
40	AMPHOTERICIN B	1397-89-3
41	ANILAZINE	101-05-3
42	ANTHRAQUINONE	84-65-1
43	AROCLOR 1254	11097-69-1
44	ATRAZINE	1912-24-9
45	5-AZACYTIDINE	320-67-2
46	AZATHIOPRINE	446-86-6

TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
47	AZOXYMETHANE	25843-45-2
48	BARIUM CHLORIDE DIHYDRATE	10326-27-9
49	BENOMYL	17804-35-2
50	BENZENE SULFONIC ACID	98-11-3
51	BENZIMIDAZOLE	51-17-2
52	BENZIMIDAZOL-2-YLUREA	24370-25-0
53	BENZOIC ACID	65-85-0
54	BENZO(E)PYRENE	192-97-2
55	BENZOTRIAZOLE	27556-51-0
56	BENZOYL CHLORIDE	98-88-4
57	BERYLLIUM SULFATE TETRAHYDRATE	7787-56-6
58	1,3-BIS(TERT-BUTYLDIOXYISOPROPYL)BENZENE	2212-81-9
59	BIS(1,5-CYCLOOCTADIENE) NICKEL	1295-35-8
60	BIS(CYCLOPENTADIENYL)VANADIUM CHLORIDE	12083-48-6
61	BIS(2-ETHYLHEXYL)ISOPHTHALATE	137-89-3
62	BIS T-BUTYLDIOXYISOPROPYLBENZENE	25155-25-3
63	(4,4'-BITHIAZOLE)-2,2'-DIAMINE	58139-59-6
64	BIUREA	110-21-4
65	BROMOCHLOROACETALDEHYDE	BROMOCHLOR
66	BROMOCHLOROACETONITRILE	83463-62-1
67	BROMOPICRIN	464-10-8
68	1-BROMO-2-PROPANOL	19686-73-8
69	1,3-BUTADIENE	106-99-0
70	2-(2-BUTOXYETHOXY)ETHYL THIOCYANATE	112-56-1
71	TERT-BUTYL CHROMATE	1189-85-1
72	N-BUTYL GLYCIDYL ETHER	2426-08-6
73	T-BUTYL GLYCIDYL ETHER	7665-72-7
74	T-BUTYL PHENYL GLYCIDYL ETHER	3101-60-8
75	BUTYRIC ACID	107-92-6
76	CARBARSONE	121-59-5
77	4-(3-CARBAZOYLAMINO)PHENOL	86-72-6
78	CARBON TETRACHLORIDE	56-23-5
79	CARMINIC ACID	1260-17-9
80	4-(CHLOROACETYL)ACETANILIDE	140-49-8
81	N-(3-CHLOROALLYL)HEXAMINIUM CHLORIDE	4080-31-3
82	4-CHLORO-2-(2,4-DINITROANILINO)PHENOL	6358-18-5
83	CHLORONEB	2675-77-6
84	1-CHLORO-1-NITROPROPANE	600-25-9
85	2-CHLORO-2-NITRO-PROPANE	594-71-8
86	2-CHLORO-1,3-PROPANEDIOL	497-04-1
87	1-CHLORO-2-PROPANOL	127-00-4
88	2-CHLORO-1-PROPANOL	78-89-7
89	3-CHLORO-1-PROPANOL	627-30-5
90	O-CHLOROSTYRENE	2039-87-4
91	CHLOROTHIAZIDE	58-94-6
92	CHLOROTHIOFORMIC ACID	EMTDP-49

TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
93	CHROMIUM CARBONYL	13007-92-6
94	C. I. DIRECT BLACK 114	61703-05-7
95	C. I. DIRECT ORANGE 6	6637-88-3
96	C. I. PIGMENT ORANGE 7	5850-81-7
97	C. I. PIGMENT RED 2	6041-94-7
98	C. I. PIGMENT RED 8	6410-30-6
99	C. I. PIGMENT RED 69	5850-90-8
100	C. I. DISPERSE BLUE 27	15791-78-3
101	CINNAMALDEHYDE ETHYLENE GLYCOL ACETAL	5660-60-6
102	CLONITRALID	1420-04-8
103	COBALTOCENE	1277-43-6
104	COUMAPHOS	56-72-4
105	M-CRESIDINE	102-50-1
106	P-CRESIDINE	120-71-8
107	O-CRESYL GLYCIDYL ETHER	2210-79-9
108	4-CUMYLPHENYLDIPHENYL PHOSPHATE (CPDPP MIXED ISOMERS)	50851-28-0
109	P-CUMYL PHENYL GLYCIDYL ETHER	61578-04-9
110	1, 2-CYCLOHEXANEDICARBOXYLIC ACID, BIS(OXIRANYLMETHYL) ESTER	5493-45-8
111	CYCLOHEXIMIDE	66-81-9
112	CYCLOSPORIN A	59865-13-3
113	CYTARABINE	147-94-4
114	CYTEMBENA	21739-91-3
115	D AND C YELLOW NO. 11	8003-22-3
116	DECANOIC ACID	334-48-5
117	DEHYDROEMETINE HYDROCHLORIDE	4914-30-1
118	2, 4-DIAMINOANISOLE SULFATE	39156-41-7
119	3, 4-DIAMINOTOLUENE	496-72-0
120	DIBROMOACETALDEHYDE	3039-13-2
121	DIBUTYL PHENYL PHOSPHATE	2528-36-1
122	DICHLORAN	99-30-9
123	DICHLOROACETALDEHYDE	79-02-7
124	5, 6-DICHLORO-2-BENZOTHIAZOLAMINE	24072-75-1
125	CIS-1, 2-DICHLOROETHYLENE	156-59-2
126	4, 5-DICHLORO-6-METHYL-2-METHYL-SULFONYLPYRIMIDINE	17901-16-5
127	1, 3-DICHLORO-2-PROPANOL	96-23-1
128	2, 3-DICHLOROPROPYLENE	78-88-6
129	DICHLORVOS	62-73-7
130	5-DIETHYLAMINO-2-NITROSO-4-METHYLPHENOL	6265-09-4
131	5-DIETHYLAMINO-2-NITROSOPHENOL HCL	25953-06-4
132	3-DIETHYLAMINOPHENOL	91-68-9
133	N, N'-DIETHYLCARBANILIDE	85-98-3
134	DIETHYLDICHLOROSILANE	1719-53-5
135	DIETHYLENE GLYCOL BIS-GLYCIDYL ETHER	4206-61-5
136	2, 2'-DIETHYLHEXYLAMINE	106-20-7
137	N, N-DIETHYL-4-((5-NITRO-2-THIAZOLYL)AZO) BENZENAMINE	54289-46-2
138	N, N-DIETHYL-P-PHENYLENEDIAMINE	93-05-0

TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
139	DIGITONIN	11024-24-1
140	3, 3'-DIHYDROXYBENZIDINE	2373-98-0
141	DIHYDROXYUREA	686-68-0
142	DI(ISOPROPYLPHENYL)PHENYL PHOSPHATE (DIPP)	28109-00-4
143	2, 4-DIMETHOXYANILINE HYDROCHLORIDE	54150-69-5
144	4, 4'-DIMETHOXYDIPHENYLAMINE	101-70-2
145	4-DIMETHYLAMINOAZOBENZENE	60-11-7
146	3-DIMETHYLAMINO-4-METHYLPHENOL	119-31-3
147	5-DIMETHYLAMINO-2-NITROSO-4-METHYLPHENOL	6265-11-8
148	3, 3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE	612-82-8
149	TRANS-1, 3-DIMETHYLCYCLOPENTANE	1759-58-6
150	1, 1-DIMETHYL-1-(2-HYDROXYPROPYLAMINE)TETRADECANIMIDE	38848-76-9
151	1, 2-DIMETHYL-3-NITROBENZENE	83-41-0
152	1, 2-DIMETHYL-4-NITROBENZENE	99-51-4
153	1, 3-DIMETHYL-2-NITROBENZENE	81-20-9
154	1, 3-DIMETHYL-4-NITROBENZENE	89-87-2
155	1, 3-DIMETHYL-5-NITROBENZENE	99-12-7
156	1, 4-DIMETHYL-2-NITROBENZENE	89-58-7
157	N, N-DIMETHYL-P-PHENYLENEDIAMINE	99-98-9
158	DIMETHYL SULFOXIDE	67-68-5
159	N, N'-DI-2-NAPTHYL-P-PHENYLENEDIAMINE	93-46-9
160	2, 4-DINITROANILINE	97-02-9
161	2-(2, 4-DINITROANILINO)PHENOL	6358-23-2
162	2, 5-DINITRO-9H-FLUORENE	15110-74-4
163	2, 7-DINITRO-9H-FLUOREN-9-ONE	31551-45-8
164	2, 4-DINITRO-6-(1-METHYLHEPTYL)PHENOL	3687-22-7
165	1, 3-DINITRONAPHTHALENE	606-37-1
166	1, 8-DINITRONAPHTHALENE	602-38-0
167	1, 5-DINITRONAPHTHALENE	605-71-0
168	2, 4-DINITROPHENOL	51-28-5
169	4, 4'-DIOCTYLDIPHENYLAMINE	101-67-7
170	N, N'-DIPHENYL-P-PHENYLENEDIAMINE	74-31-7
171	ASYM-DIPHENYLUREA	603-54-3
172	DI-SEC-BUTANOLAMINE	21838-75-5
173	N, N'-DI-SEC-BUTYL-P-PHENYLDIAMINE	101-96-2
174	ECONAZOLE	27220-47-9
175	2, 3-EPOXYBUTANE	3266-23-7
176	1, 2-EPOXY-3-BUTENE	930-22-3
177	1, 2-EPOXYDECANE	2404-44-6
178	2, 3-EPOXY-1, 4-DICHLOROBUTANE	3583-47-9
179	2, 3-EPOXY-2, 3-DIMETHYLBUTANE	5076-20-0
180	1, 2-EPOXYDODECANE	2855-19-8
181	1, 2-EPOXY-3-FLUOROPROPANE	503-09-3
182	1, 2-EPOXY-1, 1, 2, 3, 3, 3-HEXAFLUOROPROPANE	428-59-1
183	1, 2-EPOXYOCTADECANE	7390-81-0
184	9, 10-EPOXYOCTADECANOIC ACID, 2-ETHYLHEXYL ESTER	141-38-8

TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
185	1,2-EPOXYTETRADECANE	3234-28-4
186	ETHINYLESTRADIOL	57-63-6
187	ETHIONAMIDE	536-33-4
188	N-(3-ETHOXYPHENYL)ACETAMIDE	591-33-3
189	ETHYL ACETATE	141-78-6
190	ETHYL CHLORIDE	75-00-3
191	S-(ETHYL)CHLOROTHIOFORMIC ACID	2941-64-2
192	1-ETHYL-4-(DIETHYLDIAMINE)PIPERAZINE	EMTDP-59
193	N-ETHYL-N,N-DIPHENYLUREA	18168-01-9
194	S-ETHYL DIPROPYLTHIOCARBAMATE	759-94-4
195	ETHYLENE OXIDE	75-21-8
196	N-ETHYLENE-TETRAETHYLPENTAMINE	EMTDP-57
197	2-ETHYLHEXANAL	123-05-7
198	2-ETHYL-2-HEXENAL	645-62-5
199	2-ETHYLHEXENAL	26266-68-2
200	2-ETHYLHEXYLAMINE	104-75-6
201	2-ETHYLHEXYL GLYCIDYL ETHER	2461-15-6
202	3-((ETHYLHEXYL)OXY)PROPIONITRILE	10213-75-9
203	3-((ETHYLHEXYL)OXY)PROPYLAMINE	5397-31-9
204	ETHYLHYDROXY HEXANOIC ACID	29671-57-6
205	N-ETHYL-4-NITROANILINE	3665-80-3
206	N-ETHYL-O-TOLUENESULFONAMIDE	1077-56-1
207	FD AND C RED NO. 32	3118-97-6
208	FD & C YELLOW NO. 6	2783-94-0
209	FENDILINE	13042-18-7
210	FERRIC AMMONIUM FERROCYANIDE	25869-00-5
211	FORMANILIDE	103-70-8
212	GLYCIDYL ACRYLATE	106-90-1
213	GLYCIDYL METHACRYLATE	106-91-2
214	GRISEOFULVIN	126-07-8
215	1,2,3,4,6,7-HEXABROMONAPHTHALENE	75625-24-0
216	1,2,3,6,7,8-HEXACHLORODIBENZO-P-DIOXIN	57653-85-7
217	HEXACHLORONAPHTHALENE	1335-87-1
218	1,1,1,3,3,3-HEXAFLUORO-2-PROPANOL	920-66-1
219	1,3,6-HEXANETRICARBONITRILE	1772-25-4
220	HEXYL GLYCIDYL ETHER	5926-90-9
221	HYCANTHONE METHANESULFONATE	23255-93-8
222	HYDROCYANIC ACID	74-90-8
223	HYDROXYLAMINE, HYDROCHLORIDE	5470-11-1
224	8-HYDROXYQUINOLINE SULFATE	134-31-6
225	IODOACETIC ACID	64-69-7
226	IODOCHLOROHYDROXYQUINOLINE	130-26-7
227	ISOBUTYL ALCOHOL	78-83-1
228	ISODECYL METHACRYLATE	29964-84-9
229	ISOPHTHALIC DIGLYCIDYL ESTER	7195-43-9
230	P-ISOPROPOXYDIPHENYLAMINE	101-73-5

TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
231	LANTHANUM NITRATE HEXAHYDRATE	10277-43-7
232	LAURIC ACID	143-07-7
233	LAURYL GLYCIDYL ETHER	2461-18-9
234	LEUCO VAT BLUE 1	6537-68-4
235	LITHOCHOLIC ACID	434-13-9
236	LUMINOL	521-31-3
237	MALAOXON	1634-78-2
238	DL-MENTHOL	15356-70-4
239	2-MERCAPTO-4-METHYL-5-THIAZOLYL METHYL KETONE	7725-93-1
240	4-METHOXYBENZILIDINE-4'-N-BUTYLANILINE (MBBA)	26227-73-6
241	3-((METHOXYCARBONYL)AMINO)PHENYL N-(3-METHYLPHENYL)CARBAMATE	13684-63-4
242	METHOXYETHYL MERCURY CHLORIDE	123-88-6
243	METHOXYFLURANE	76-38-0
244	3-METHYLAMINO-4-METHYLPHENOL	6265-13-0
245	METHYL-2 BENZIMIDAZOLE CARBAMATE	METHYL-2 B
246	4-(6-METHYL-2-BENZOTHIAZOLYL)-BENZENAMINE	92-36-4
247	METHYL BROMIDE	74-83-9
248	METHYL DEMETON	8022-00-2
249	N'-METHYL-N,N-DIPHENYLUREA	13114-72-2
250	METHYLENEBIS(4-CYCLOHEXYL ISOCYANATE)	5124-30-1
251	2,2'-METHYLENE BIS(PHENYLENEOXYMETHYLENE)BISOXIRANE	39817-09-9
252	METHYLENE BIS(THIOCYANATE)	6317-18-6
253	METHYLENEDIANILINE	101-77-9
254	METHYLETHYL KETONE	78-93-3
255	METHYLGLUTARONITRILE	4553-62-2
256	METHYL GLYCIDYL ETHER	930-37-0
257	METHYL MERCURIC CHLORIDE	115-09-3
258	METHYLMERCURY HYDROXIDE	1184-57-2
259	2-METHYL-3-NITROANILINE	603-83-8
260	2-METHYL-4-NITROANILINE	99-52-5
261	2-METHYL-6-NITROANILINE	570-24-1
262	4-METHYL-2-NITROANILINE	89-62-3
263	4-METHYL-3-NITROANILINE	119-32-4
264	5-METHYL-2-NITROANILINE	578-46-1
265	N-METHYL-4-NITROANILINE	100-15-2
266	2-METHYL-3-NITRO-BENZOIC ACID	1975-50-4
267	3-METHYL-2-NITRO-BENZOIC ACID	5437-38-7
268	3-METHYL-4-NITRO-BENZOIC ACID	3113-71-1
269	4-METHYL-3-NITRO-BENZOIC ACID	96-98-0
270	5-METHYL-2-NITRO-BENZOIC ACID	3113-72-2
271	2-METHYL-5-NITROBENZOIC ACID	1975-52-6
272	2-METHYL-6-NITROBENZOIC ACID	13506-76-8
273	METHYLTIN-TRIS(ISOOCTYLMERCAPTOACETATE)	54849-38-6
274	METHYLTRIFLUOROMETHANESULFONATE	333-27-7
275	METRONIDAZOLE	443-48-1
276	MEXACARBATE	315-18-4

TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
277	MICHLER'S KETONE	90-94-8
278	MOLYBDENUM TRIOXIDE	1313-27-5
279	MONOSODIUM GLUTAMATE	142-47-2
280	4-(2-NAPHTHYLAMINO)PHENOL	93-45-8
281	ALPHA-NAPHTHYL ISOTHIOCYANATE	551-06-4
282	2-NAPHTHYL LACTATE	93-43-6
283	NEODECANOIC ACID, 2,3-EPOXYPROPYL ESTER	26761-45-5
284	NEOPENTYL GLYCOL DIGLYCIDYL ETHER	17557-23-2
285	NICKEL CARBONYL	13463-39-3
286	NIFEDIPINE	21829-25-4
287	NTA(NITRILOTRIACETIC ACID)	139-13-9
288	9-NITROANTHRACENE	602-60-8
289	4-NITRO-1,3-BENZENEDIAMINE	5131-58-8
290	O-NITROBENZOIC ACID	552-16-9
291	O-NITROBENZOYL CHLORIDE	610-14-0
292	M-NITROBENZYL CHLORIDE	619-23-8
293	2-NITRO-1-BUTANOL	609-31-4
294	2-NITRODIPHENYLAMINE	119-75-5
295	2-NITROETHANOL	625-48-9
296	3-NITRO-9-FLUORENONE	42135-22-8
297	1-NITRO-2-METHYLNAPHTHALENE	881-03-8
298	P-NITROPHENETHYL ALCOHOL, ACETATE	104-30-3
299	O-NITROPHENETHYL ALCOHOL, ACETATE	833-43-2
300	1-(4-NITROPHENYL)-2-CHLOROPROPANE	34197-98-3
301	2-NITRO-P-PHENYLENEDIAMINE	5307-14-2
302	4-NITROPHTHALIC ANHYDRIDE	5466-84-2
303	3-NITROPROPIONIC ACID	504-88-1
304	1-NITROPYRENE	5522-43-0
305	N-NITROSODIETHYLAMINE	55-18-5
306	N-NITROSODIPHENYLAMINE	86-30-6
307	N-NITROSO-N-ETHYLURETHANE	614-95-9
308	4-NITROSOPHENOL	104-91-6
309	BETA-NITROSTYRENE	102-96-5
310	5-NITRO-O-TOLUIDINE	99-55-8
311	NONAMETHYLENEIMINE	4396-27-4
312	NONYLPHENYL DIPHENYL PHOSPHATE (NPDPP MIXED ISOMERS)	64532-97-4
313	NOSCAPINE	128-62-1
314	OCTACHLORONAPHTHALENE	2234-13-1
315	OCTANOIC ACID	124-07-2
316	2-OCTYL-3-ISOTHIAZOLONE	26530-20-1
317	P-N-OCTYLOXYBENZOIC ACID	2493-84-7
318	OLEIC ACID DIETHANOLAMINE	13961-86-9
319	OLIVETOL	500-66-3
320	PENTAETHYLPENTAMINE	EMTDP-56
321	1-PENTANOL	71-41-0
322	3-PENTENENITRILE	4635-87-4

TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
323	2-PENTENENITRILE	13284-42-9
324	2-(P-PENTYLPHENYL)-5-(P-PENTYLOXYPHENYL) PYRIMIDINE	34913-07-0
325	PERCHLOROMETHYL MERCAPTAN	594-42-3
326	PHENANTHRENE	85-01-8
327	P-PHENETIDINE	156-43-4
328	M-PHENETIDINE	621-33-0
329	O-PHENYLENEDIAMINE	95-54-5
330	M-PHENYLENEDIAMINE	108-45-2
331	P-PHENYLENEDIAMINE DIHYDROCHLORIDE	624-18-0
332	PHENYL GLYCIDYL ETHER	122-60-1
333	N-PHENYL-1-NAPHTHYLAMINE	90-30-2
334	PHENYLPHOSPHINE	638-21-1
335	PICRYL CHLORIDE	88-88-0
336	POLYETHYLPOTASSIUM 2-BENZYL-4-CHLOROPHENATE	35471-49-9
337	POLYTHIAZIDE	346-18-9
338	POTASSIUM DICHROMATE	7778-50-9
339	POTASSIUM P-TERT AMYLPHENATE	53404-18-5
340	TETRACHROMIC ACID, POTASSIUM ZINC SALT	12433-50-0
341	PROCARBAZINE HYDROCHLORIDE	366-70-1
342	PROGESTERONE	57-83-0
343	2-PROPANOL, 1-CHLORO-, PHOSPHATE (3:1)	13674-84-5
344	S-(N-PROPYL)CHLOROTHIOFORMIC ACID	EMTDP-51
345	PROPYLENE	115-07-1
346	PROPYLENE CYANOHYDRIN	2567-01-3
347	PYRENE	129-00-0
348	QUINACRINE DIHYDROCHLORIDE	69-05-6
349	QUINACRINE MUSTARD	4213-45-0
350	QUINETHAZONE (AQUAMOX)	73-49-4
351	RESCINNAMINE	24815-24-5
352	SCOPOLAMINE HYDROBROMIDE	114-49-8
353	SODIUM CHLORIDE	7647-14-5
354	SODIUM CYANURATE	2624-17-1
355	SODIUM IODOMETHANESULFONATE	126-31-8
356	STEARATOCHROMIC CHLORIDE COMPLEX	15242-96-3
357	STYRENE	100-42-5
358	SULFISOXAZOLE	127-69-5
359	1,2,4,5-TETRABROMO-3,6-DIMETHYLBENZENE	23488-38-2
360	TETRACHLORONAPHTHALENE	1335-88-2
361	2,3,5,6-TETRACHLORO-4-NITROANISOLE	2438-88-2
362	2,3,4,6-TETRACHLOROPHENOL	58-90-2
363	2,3,4,5-TETRACHLOROPHENOL	4901-51-3
364	2,3,5,6-TETRACHLOROPHENOL	935-95-5
365	TETRADECANOIC ACID	544-63-8
366	TETRAFLUOROETHYLENE	116-14-3
367	N,N,N',N'-TETRAMETHYL-P-PHENYLENEDIAMINE	100-22-1
368	1,3,6,8-TETRANITROPYRENE	28767-61-5

TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
369	THIABENDAZOLE	148-79-8
370	THIAZOLE	288-47-1
371	THIOACETAMIDE	62-55-5
372	THIOPHANATE M	23564-05-8
373	THIOUREA	62-56-6
374	TITANIUM DIOXIDE	13463-67-7
375	D-ALPHA-TOCOPHERYL SUCCINATE	4345-03-3
376	TOLAZAMIDE	1156-19-0
377	O-TOLUALDEHYDE	529-20-4
378	2,6-TOLUENEDIAMINE DIHYDROCHLORIDE	15481-70-6
379	2,5-TOLUENEDIAMINE SULFATE	6369-59-1
380	M-TOLUIDINE	108-44-1
381	M-TOLUIDINE HYDROCHLORIDE	638-03-9
382	P-TOLUNITRILE	104-85-8
383	TRIALLYL ISOCYANURATE	1025-15-6
384	TRIBENZYL ISOCYANURATE	606-03-1
385	TRIBROMOACETONITRILE	TRIBROMOAC
386	2,4,6-TRIBROMOPHENYL CARBONATE	67990-32-3
387	TRI-SEC-BUTANOLAMINE	2421-02-5
388	TRICHLOROMELAMINE	7673-09-8
389	2,3,4-TRICHLORONITROBENZENE	17700-09-3
390	2,4,5-TRICHLORONITROBENZENE	89-69-0
391	2,4,6-TRICHLORONITROBENZENE	18708-70-8
392	3,4,6-TRICHLORO-2-NITROPHENOL	82-62-2
393	2,3,4-TRICHLOROPHENOL	15950-66-0
394	2,3,5-TRICHLOROPHENOL	933-78-8
395	2,3,6-TRICHLOROPHENOL	933-75-5
396	3,4,5-TRICHLOROPHENOL	609-19-8
397	P-TRITOLYL PHOSPHATE	78-32-0
398	O-TRITOLYL PHOSPHATE	78-30-8
399	TRIETHYLENE GLYCOL DIGLYCIDYL ETHER	1954-28-5
400	TRIFLUOROTHYMIDINE	70-00-8
401	1,8,9-TRIHYDROXYANTHRACENE	480-22-8
402	TRIMETHYL ISOCYANURATE	827-16-7
403	2,4,6-TRINITROANILINE	489-98-5
404	1,3,6-TRINITROPYRENE	75321-19-6
405	2,4,6-TRINITROTOLUENE	118-96-7
406	TRIPHENYLTIN HYDROXIDE	76-87-9
407	TRI-N-PROPYLAMINE	102-69-2
408	TRIS(CARBAMOYLMETHYL)ISOCYANURATE	1843-48-7
409	TRIS(3-CHLORO-2-HYDROXYPROPYL)ISOCYANURATE	7423-53-2
410	TRIS (2,3-EPOXYPROPYL) ISOCYANURATE	2451-62-9
411	TRIS(2-ETHYLHEXYL)TRIMELLITATE	3319-31-1
412	1,3,5-TRIS(2-HYDROXYETHYL)TRIAZINE-2,4,6-TRIONE	839-90-7
413	TRIS(2-KETOPROPYL)ISOCYANURATE	61050-97-3
414	TRIS(TRIPHENYLSTANNYL)ISOCYANURATE	752-74-9

TABLE 2

CHEMICALS SELECTED FOR MUTAGENICITY TESTING IN SALMONELLA IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
415	URETHANE	51-79-6
416	VERAPAMIL	52-53-9
417	1-VINYL-4-(DIETHYLDIAMINE)PIPERAZINE	EMTDP-58
418	VINYLIDENE FLUORIDE	75-38-7
419	VITAMIN D	1406-16-2
420	WATER	7732-18-5
421	XYLENES, COMMERCIAL MIXTURE	1330-20-7
422	ZIRCONOCENE DICHLORIDE	1291-32-3

TABLE 3

CHEMICAL TEST RESULTS FOR HERITABLE GENETIC EFFECTS IN DROSOPHILA IN FY 1984

SEQ. NO.	CHEMICAL	RESULTS *		CAS NO.
		SLRL	** RT	
1	ACROLEIN	-	ND	107-02-8
2	BENZALDEHYDE	-	ND	100-52-7
3	BROMOFORM	+	-	75-25-2
4	CHLORAMBUCIL	+	+	305-03-3
5	3-CHLOROMETHYLPYRIDINE HYDROCHLORIDE	-	ND	6959-48-4
6	C.I. ACID RED 114	-	ND	6459-94-5
7	CINNAMALDEHYDE	+	-	104-55-2
8	COUMARIN	-	ND	91-64-5
9	DIBUTYLTIN DIACETATE	-	ND	1067-33-0
10	DICHLORAN	?	ND	99-30-9
11	DI(2-ETHYLHEXYL)ADIPATE	-	ND	103-23-1
12	1,8-DIHYDROXY-4,5-DINITROANTHRAQUINONE	?	ND	81-55-0
13	7,12-DIMETHYLBENZ(A)ANTHRACENE	+/-	+/+	57-97-6
14	2,4-DINITROANILINE	-	ND	97-02-9
15	1,2-EPOXY-3,3,3-TRICHLOROPROPANE	+	-	3083-23-6
16	S-ETHYL DIPROPYLTHIOCARBAMATE	-	ND	759-94-4
17	ETHYLENE THIOUREA	?	ND	96-45-7
18	FORMALDEHYDE	+	+	50-00-0
19	GLUTARALDEHYDE	-	ND	111-30-8
20	HALOTHANE	+	-	151-67-7
21	HC YELLOW 4	+	-	52551-67-4
22	HEXAMETHYL-P-ROSANILINE CHLORIDE	?	ND	548-62-9
23	METHYL ACRYLATE	-	ND	96-33-3
24	MONO(2-ETHYLHEXYL)PHTHALATE	-	ND	4376-20-9
25	NTA(NITRILOTRIACETIC ACID)	?	ND	139-13-9
26	P-NITROANILINE	-	ND	100-01-6
27	N-NITROSODIMETHYLAMINE	+, +	+, -	62-75-9
28	PHENOL	-	ND	108-95-2
29	O-PHENYLPHENOL	-	ND	90-43-7
30	PICRIC ACID	+, -	-, ND	88-89-1
31	QUINOLINE	-	ND	91-22-5
32	SAFROLE	-	ND	94-59-7
33	1,1,2,2-TETRACHLOROETHANE	-	ND	79-34-5
34	TETRAETHYLENEPENTAMINE	?	ND	112-57-2
35	O-TOLUIDINE HYDROCHLORIDE	-	ND	636-21-5
36	TRIS(2-CHLOROETHYL)PHOSPHITE	-	ND	140-08-9
37	2,6-XYLIDINE	-	ND	87-62-7

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE

** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

SLRL = SEX-LINKED RECESSIVE LETHAL, RT = RECIPROCAL TRANSLOCATION

ND = NOT DONE

TABLE 4

CHEMICALS SELECTED TO BE TESTED FOR HERITABLE GENETIC EFFECTS IN DROSOPHILA IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
1	ACRYLONITRILE	107-13-1
2	AMPHETAMINE SULFATE	60-13-9
3	BENZO(A)PYRENE	50-32-8
4	BIS(2-CHLOROETHYL)ETHER	111-44-4
5	1,3-BUTADIENE	106-99-0
6	1,4-BUTANEDIOL DIGLYCIDYL ETHER	2425-79-8
7	CHLORAMPHENICOL SODIUM SUCCINATE	982-57-0
8	MONOCHLOROACETIC ACID	79-1[illegible]-8
9	1-CHLORO-2-PROPANOL	127-00-4
10	C. I. BASIC ORANGE 2	532-82-1
11	2,3-DIBROMO-2-BUTENE-1,4-DIOL	3234-02-4
12	DIMETHYLETHANOLAMINE	108-01-0
13	DIMETHYL METHYLPHOSPHONATE	756-79-6
14	DIMETHYL MORPHOLINOPHOSPHORAMIDATE	597-25-1
15	DIMETHYLOLDIHYDROXYETHYLENEUREA	1854-26-8
16	DIMETHYLVINYL CHLORIDE	513-37-1
17	EPIBROMOHYDRIN	3132-64-7
18	EUGENOL	97-53-0
19	FURAN	110-00-9
20	GLYCIDOL	556-52-5
21	HYDROQUINONE	123-31-9
22	N-(HYDROXYETHYL)ETHYLENEDIAMINE	111-41-1
23	2-HYDROXY-1,4-NAPHTHOQUINONE	83-72-7
24	ISATIN-5-SULFONIC ACID SODIUM SALT	80789-74-8
25	ISOPRENE	78-79-5
26	MONOISOPROPANOLAMINE	78-96-6
27	ISOPROPYL GLYCIDYL ETHER	4016-14-2
28	MALTOL	118-71-8
29	MERCURIC CHLORIDE	7487-94-7
30	METHACRYLONITRILE	126-98-7
31	METHYL CARBAMATE	598-55-0
32	OXYTETRACYCLINE HYDROCHLORIDE	2058-46-0
33	PENTAETHYLENEHEXAMINE	4067-16-7
34	PHENESTERIN	3546-10-9
35	RESERPINE	50-55-5
36	RESORCINOL	108-46-3
37	ROXARSONE	121-19-7
38	TETRACYCLINE HYDROCHLORIDE	64-75-5
39	TRIETHYLENETETRAMINE	112-24-3

TABLE 5

CHEMICAL TEST RESULTS FOR MUTAGENICITY IN L5178Y MOUSE LYMPHOMA CELLS IN FY 1984

SEQ. NO.	CHEMICAL	RESULTS * **	CAS NO.
1	4-ACETYLAMINOFLUORENE	+	28322-02-3
2	2-AMINO-4-NITROPHENOL	+	99-57-0
3	3-AMINOTRIAZOLE	-	61-82-5
4	AMPICILLIN TRIHYDRATE	-	7177-48-2
5	ANILINE	+, +	62-53-3
6	BENZALDEHYDE	+	100-52-7
7	BENZENE	-	71-43-2
8	BENZOFURAN	+	271-89-6
9	BENZYL ALCOHOL	+	100-51-6
10	BENZYL CHLORIDE	+	100-44-7
11	BROMODICHLOROMETHANE	+	75-27-4
12	BROMOFORM	+	75-25-2
13	2-BUTANONE PEROXIDE	+	1338-23-4
14	TERT-BUTYL ALCOHOL	-	75-65-0
15	N-BUTYL CHLORIDE	+	109-69-3
16	CALCIUM CHROMATE	+	13765-19-0
17	CARISOPRODOL	+	78-44-4
18	CHLORENDIC ACID	+	115-28-6
19	MONOCHLOROACETIC ACID	+	79-11-8
20	P-CHLOROANILINE	+, +	106-47-8
21	O-CHLOROBENZALMALONONITRILE (CS)	+	2698-41-1
22	CHLOROBENZILATE	-	510-15-6
23	2-CHLOROETHANOL (ETHYLENE CHLOROHYDRIN)	+	107-07-3
24	3-CHLOROMETHYLPYRIDINE HYDROCHLORIDE	+	6959-48-4
25	CINNAMYL ANTHRANILATE	+	87-29-6
26	CYCLOHEXANONE	-	108-94-1
27	DECABROMODIPHENYL OXIDE	-	1163-19-5
28	2,4-DIAMINOPHENOL DIHYDROCHLORIDE	+	137-09-7
29	2,3-DIBROMO-1-PROPANOL	+	96-13-9
30	2,4-DICHLOROPHENOL	+	120-83-2
31	DICHLORVOS	+	62-73-7
32	N,N′-DICYCLOHEXYLTHIOUREA	+	1212-29-9
33	1,2:3,4-DIEPOXYBUTANE DL	+	298-18-0
34	DI(2-ETHYLHEXYL) PHTHALATE	-	117-81-7
35	DIETHYLSTILBESTROL	+	56-53-1
36	N,N-DIMETHYLANILINE	+	121-69-7
37	DIMETHYLFORMAMIDE	+	68-12-2
38	DIMETHYL HYDROGEN PHOSPHITE	+	868-85-9
39	DIMETHYL METHYLPHOSPHONATE	+	756-79-6
40	DIMETHYL MORPHOLINOPHOSPHORAMIDATE	+	597-25-1
41	DIMETHYLVINYL CHLORIDE	+	513-37-1
42	1,2-EPOXYBUTANE	+	106-88-7

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE

** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

TABLE 5

CHEMICAL TEST RESULTS FOR MUTAGENICITY IN L5178Y MOUSE LYMPHOMA CELLS IN FY 1984

SEQ. NO.	CHEMICAL	RESULTS * **	CAS NO.
43	ERYTHROMYCIN STEARATE	?	643-22-1
44	ETHYLENE GLYCOL	+	107-21-1
45	FURFURAL	+	98-01-1
46	GLUTARALDEHYDE	+	111-30-8
47	GLYCIDOL	+	556-52-5
48	HAMAMELIS WATER (WITCH HAZEL)	-	68916-39-2
49	HC BLUE 1	+	2784-94-3
50	HEXYLRESORCINOL	+	136-77-6
51	HYDROCHLOROTHIAZIDE	+	58-93-5
52	HYDROQUINONE	+	123-31-9
53	8-HYDROXYQUINOLINE	+	148-24-3
54	IODINATED GLYCEROL	+	5634-39-9
55	ISOPHORONE	+	78-59-1
56	MALONALDEHYDE, SODIUM SALT	+	24382-04-5
57	METHYL METHACRYLATE	+	80-62-6
58	NALIDIXIC ACID	-	389-08-2
59	NITROFURAZONE	+	59-87-0
60	OXYTETRACYCLINE HYDROCHLORIDE	+	2058-46-0
61	PENICILLIN V	-	87-08-1
62	PENTACHLOROANISOLE	+	1825-21-4
63	PHENACETIN	-	62-44-2
64	PHENOXY ACETIC ACID	-	122-59-8
65	PHENYLBUTAZONE	+	50-33-9
66	PHENYLEPHRINE HYDROCHLORIDE	+	61-76-7
67	O-PHENYLPHENOL	+, +	90-43-7
68	POTASSIUM FLUORIDE	+	7789-23-3
69	PYRIDINE	-	110-86-1
70	RESORCINOL	+	108-46-3
71	RHODAMINE 6G	+	989-38-8
72	SAFROLE	+	94-59-7
73	SODIUM BIFLUORIDE	+, +	51273-71-3
74	SODIUM CHLORIDE	-	7647-14-5
75	SODIUM FLUORIDE	+	7681-49-4
76	STYRENE OXIDE	+	96-09-3
77	SUCROSE	-	57-50-1
78	TETRACHLOROETHYLENE	-	127-18-4
79	TETRACYCLINE HYDROCHLORIDE	+	64-75-5
80	TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM CHLORIDE	+	124-64-1
81	TOLUENE (TECHNICAL)	?	108-88-3
82	TRICHLORFON	+	52-68-6
83	VINYL CYCLOHEXENE DIEPOXIDE	+	106-87-6
84	VINYL TOLUENE	+	25013-15-4
85	WATER	-, -	7732-18-5

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE

** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

TABLE 6
CHEMICALS SELECTED TO BE TESTED FOR MUTAGENICITY IN L5178Y MOUSE LYMPHOMA CELLS IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
1	4-ACETYLAMINOFLUORENE	28322-02-3
2	ALLYL ISOTHIOCYANATE	57-06-7
3	3-AMINOTRIAZOLE	61-82-5
4	11-AMINOUNDECANOIC ACID	2432-99-7
5	L-ASCORBIC ACID	50-81-7
6	BARIUM CHLORIDE DIHYDRATE	10326-27-9
7	BENZYL ACETATE	140-11-4
8	2-BIPHENYLAMINE HYDROCHLORIDE	2185-92-4
9	BIS(2-CHLORO-1-METHYLETHYL) ETHER	108-60-1
10	BISPHENOL A	80-05-7
11	BORIC ACID	10043-35-3
12	BUTYLATED HYDROXYTOLUENE	128-37-0
13	BUTYL BENZYL PHTHALATE	85-68-7
14	CADMIUM CHLORIDE	10108-64-2
15	CALCIUM CHROMATE	13765-19-0
16	CHLORDANE (TECHNICAL GRADE)	12789-03-6
17	P-CHLOROANILINE	106-47-8
18	CHLOROBENZILATE	510-15-6
19	3-CHLOROMETHYLPYRIDINE HYDROCHLORIDE	6959-48-4
20	4-CHLORO-2-NITROANILINE	89-63-4
21	CHLOROTHALONIL	1897-45-6
22	5-CHLORO-O-TOLUIDINE	95-79-4
23	CHLORPHENIRAMINE MALEATE	113-92-8
24	COCONUT DIETHANOLAMIDE	68603-42-9
25	COUMAPHOS	56-72-4
26	DIALLYL PHTHALATE	131-17-9
27	DIAZINON	333-41-5
28	DIBUTYLTIN DIACETATE	1067-33-0
29	1,4-DICHLOROBENZENE (P-DICHLOROBENZENE)	106-46-7
30	1,2-DICHLOROBENZENE (O-DICHLOROBENZENE)	95-50-1
31	DICHLORODIPHENYLETHYLENE	72-55-9
32	DICHLOROMETHANE (METHYLENE CHLORIDE)	75-09-2
33	N,N'-DICYCLOHEXYLTHIOUREA	1212-29-9
34	DIETHANOLAMINE	111-42-2
35	DI(2-ETHYLHEXYL)ADIPATE	103-23-1
36	N,N'-DIETHYLTHIOUREA	105-55-5
37	DIGLYCIDYL RESORCINOL ETHER	101-90-6
38	2,4-DIMETHOXYANILINE HYDROCHLORIDE	54150-69-5
39	1,4-DIOXANE	123-91-1
40	DIPHENHYDRAMINE HYDROCHLORIDE	147-24-0
41	ENDRIN	72-20-8
42	EPHEDRINE SULFATE	134-72-5
43	1,2-EPOXYBUTANE	106-88-7
44	1,2-EPOXYHEXADECANE	7320-37-8
45	2-ETHOXYETHANOL (EGMEE)	110-80-5
46	ETHYLENEDIAMINE TETRAACETIC ACID (EDTA)	150-38-9

TABLE 6

CHEMICALS SELECTED TO BE TESTED FOR MUTAGENICITY IN L5178Y MOUSE LYMPHOMA CELLS IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
47	ETHYLENE THIOUREA	96-45-7
48	MONO(2-ETHYLHEXYL)ADIPATE	4337-65-9
49	FERRIC CHLORIDE	7705-08-0
50	FLUOMETURON	2164-17-2
51	FURAN	110-00-9
52	FUROSEMIDE	54-31-9
53	HC BLUE 2	33229-34-4
54	HEPTACHLOR	76-44-8
55	HEXACHLOROETHANE	67-72-1
56	IRON DEXTRAN	9004-66-4
57	ISOBUTYRALDEHYDE	78-84-2
58	LAURIC ACID DIETHANOLAMINE CONDENSATE	120-40-1
59	D-LIMONENE	5989-27-5
60	MALATHION	121-75-5
61	D-MANNITOL	69-65-8
62	MELAMINE	108-78-1
63	2-MERCAPTOBENZIMIDAZOLE	583-39-1
64	MERCAPTOBENZOTHIAZOLE	149-30-4
65	MERCURIC CHLORIDE	7487-94-7
66	METHAPYRILENE HYDROCHLORIDE	135-23-9
67	ALPHA-METHYLBENZYL ALCOHOL	98-85-1
68	METHYL CARBAMATE	598-55-0
69	METHYLDOPA	555-30-6
70	METHYL VIOLOGEN	1910-42-5
71	MOLYBDENUM TRIOXIDE	1313-27-5
72	NICKEL SULFATE HEXAHYDRATE	10101-97-0
73	NITROFURANTOIN	67-20-9
74	P-NITROTOLUENE	99-99-0
75	OLEIC ACID DIETHANOLAMINE	13961-86-9
76	OXYTETRACYCLINE HYDROCHLORIDE	2058-46-0
77	PENTACHLOROETHANE	76-01-7
78	PENTACHLORONITROBENZENE	82-68-8
79	PHENAZOPYRIDINE HYDROCHLORIDE	136-40-3
80	PHENESTERIN	3546-10-9
81	PHENOL	108-95-2
82	PHTHALAMIDE	88-96-0
83	POTASSIUM CHLORIDE	7447-40-7
84	QUINOLINE	91-22-5
85	ROTENONE	83-79-4
86	ROXARSONE	121-19-7
87	SODIUM DODECYL SULFATE	151-21-3
88	SODIUM FLUORIDE	7681-49-4
89	SODIUM XYLENESULFONATE	1300-72-7
90	STANNOUS CHLORIDE	7772-99-8

TABLE 6

CHEMICALS SELECTED TO BE TESTED FOR MUTAGENICITY IN L5178Y MOUSE LYMPHOMA CELLS IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
91	SUCCINIC ACID 2,2-DIMETHYLHYDRAZIDE	1596-84-5
92	SUCROSE	57-50-1
93	4,4'-SULFONYLDIANILINE	80-08-0
94	1,1,2,2-TETRACHLOROETHANE	79-34-5
95	TETRACHLOROETHYLENE	127-18-4
96	2,3,5,6-TETRACHLORO-4-NITROANISOLE	2438-88-2
97	TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM SULFATE	55566-30-8
98	TITANIUM DIOXIDE	13463-67-7
99	2,6-TOLUENEDIAMINE DIHYDROCHLORIDE	15481-70-6
100	2,4,5-TRIMETHOXYBENZALDEHYDE	4460-86-0
101	TRIMETHYLTHIOUREA	2489-77-2
102	4-VINYLCYCLOHEXENE	100-40-3
103	VINYLIDENE CHLORIDE (1,1-DICHLOROETHYLENE)	75-35-4

TABLE 7

CHEMICAL TEST RESULTS FOR CYTOGENETIC EFFECTS IN CHINESE HAMSTER OVARY CELLS IN FY 1984

SEQ. NO.	CHEMICAL	RESULTS *		CAS NO.
		CA	** SCE	
1	ALDICARB	−	+	116-06-3
2	ALLYL GLYCIDYL ETHER	+	+	106-92-3
3	ALLYL ISOVALERATE	+	+	2835-39-4
4	9-AMINOACRIDINE HCL H20	+	+	52417-22-8
5	ANILAZINE	?	+	101-05-3
6	O-ANTHRANILIC ACID	+	+	118-92-3
7	AZODICARBONAMIDE	?	−	123-77-3
8	BARIUM CHLORIDE DIHYDRATE	−	−	10326-27-9
9	BENZETHONIUM CHLORIDE	−	−	121-54-0
10	BENZYL ALCOHOL	+	?	100-51-6
11	BISPHENOL A DIGLYCIDYL ETHER	+	+	1675-54-3
12	BORIC ACID	−	−	10043-35-3
13	BROMODICHLOROMETHANE	−	?	75-27-4
14	TERT-BUTYL ALCOHOL	−	−	75-65-0
15	N-BUTYL CHLORIDE	−	−	10[illegible]-3
16	TERT-BUTYL HYDROPEROXIDE	+	+	7[illegible]1-2
17	CARISOPRODOL	+	?	78-44-4
18	CHLORDANE (REAGENT GRADE)	−	+	57-74-9
19	2-CHLOROETHANOL (ETHYLENE CHLOROHYDRIN)	+	+	107-07-3
20	C.I. BASIC RED 9	−	+	569-61-9
21	CITRAL	−	+	5392-40-5
22	CODEINE PHOSPHATE	−	+	52-28-8
23	DICHLORVOS	+	+	62-73-7
24	N,N′-DICYCLOHEXYLTHIOUREA	−	+	1212-29-9
25	DI(2-ETHYLHEXYL) PHTHALATE	NT	+	117-81-7
26	DIETHYLSTILBESTROL	+	−	56-53-1
27	DIGLYCIDYL RESORCINOL ETHER	+	+	101-90-6
28	1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE (MONOMER)	−	+	147-47-7
29	DIMETHOXANE	+	+	828-00-2
30	DIMETHYL HYDROGEN PHOSPHITE	?	+	868-85-9
31	DIMETHYL MORPHOLINOPHOSPHORAMIDATE	+	+	597-25-1
32	DIMETHYLVINYL CHLORIDE	−	+	513-37-1
33	2,7-DINITRO-9H-FLUOREN-9-ONE	−	+	31551-45-8
34	1,5-DINITRONAPHTHALENE	+	−	605-71-0
35	DIOXATHION	−	+	78-34-2
36	EPHEDRINE SULFATE	?	?	134-72-5
37	1,2-EPOXYBUTANE	+	+	106-88-7
38	ETHYLBENZENE	−	−	100-41-4
39	MONO(2-ETHYLHEXYL)ADIPATE	+	+W	4337-65-9
40	GLYCIDOL	+	+	556-52-5
41	HEPTACHLOR	+	+	76-44-8
42	HEXANAMIDE	+	+	628-02-4

* + = POSITIVE, − = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE

** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

CA = CHROMOSOME ABERRATIONS, SCE = SISTER CHROMATID EXCHANGES

TABLE 7

CHEMICAL TEST RESULTS FOR CYTOGENETIC EFFECTS IN CHINESE HAMSTER OVARY CELLS IN FY 1984

SEQ. NO.	CHEMICAL	RESULTS *		CAS NO.
		CA	** SCE	
43	IODOFORM	-	-	75-47-8
44	ISOBUTYRALDEHYDE	+	+	78-84-2
45	ISOPHORONE	-	+	78-59-1
46	LITHOCHOLIC ACID	-	-	434-13-9
47	MERCAPTOBENZOTHIAZOLE	+	+	149-30-4
48	MERCURIC CHLORIDE	+	+W	7487-94-7
49	METHAPYRILENE HYDROCHLORIDE	+	+	135-23-9
50	METHOXYCHLOR	-	+	72-43-5
51	METHYL METHACRYLATE	+	+	80-62-6
52	MICHLER'S KETONE	-	?	90-94-8
53	MIREX	-	-	2385-85-5
54	MOLYBDENUM TRIOXIDE	-	-	1313-27-5
55	MONO(2-ETHYLHEXYL)PHTHALATE	-	+W	4376-20-9
56	NICKELOCENE	-	-	1271-28-9
57	9-NITROANTHRACENE	-	+	602-60-8
58	1-NITRO-2-METHYLNAPHTHALENE	-	+	881-03-8
59	1-NITRONAPHTHALENE	+	-	86-57-7
60	3-NITROPROPIONIC ACID	+	+	504-88-1
61	4,4'-OXYDIANILINE	+	+	101-80-4
62	PENICILLIN VK	+	+	132-98-9
63	O-PHENANTHROLINE	+	+	66-71-7
64	PHENIRAMINE MALEATE	-	-	132-20-7
65	P-PHENYLENEDIAMINE DIHYDROCHLORIDE	+	+	624-18-0
66	PHENYLEPHRINE HYDROCHLORIDE	-	+	61-76-7
67	O-PHENYLPHENOL	-	+	90-43-7
68	PICLORAM	+	+	1918-02-1
69	PROPIONALDEHYDE	+	+	123-38-6
70	PROPYLENE OXIDE	+	+	75-56-9
71	PYRIDINE	+	+	110-86-1
72	QUINOLINE	?	+	91-22-5
73	SODIUM FLUORIDE	-	+	7681-49-4
74	SUCCINIC ACID 2,2-DIMETHYLHYDRAZIDE	-	-	1596-84-5
75	TETRAETHYLTHIURAM DISULFIDE	+	-	97-77-8
76	1-TRANS-DELTA-9-TETRAHYDROCANNABINOL	-	+W	1972-08-3
77	THEOPHYLLINE	-	+	58-55-9
78	4,4-THIOBIS(6-TERT-BUTYL-M-CRESOL)	-	+	96-69-5
79	D-ALPHA-TOCOPHERYL SUCCINATE	-	+	4345-03-3
80	WATER	-,-	-,-	7732-18-5

* + = POSITIVE, - = NEGATIVE, ? = EQUIVOCAL, W = WEAK RESPONSE

** RESULTS SEPARATED BY COMMAS REPRESENT MULTIPLE TESTS

CA = CHROMOSOME ABERRATIONS, SCE = SISTER CHROMATID EXCHANGES

TABLE 8

CHEMICALS SELECTED TO BE TESTED FOR CYTOGENETIC EFFECTS IN CHINESE HAMSTER OVARY CELLS IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
1	ACETALDEHYDE	75-07-0
2	ACETIN	26446-35-5
3	ALLOXAN MONOHYDRATE	3237-50-1
4	2-AMINOANTHRACENE	613-13-8
5	3-AMINOTRIAZOLE	61-82-5
6	AMPICILLIN TRIHYDRATE	7177-48-2
7	5-AZACYTIDINE	320-67-2
8	1-AZIRIDINEETHANOL	1072-52-2
9	BENZO(A)PYRENE	50-32-8
10	BENZYL CHLORIDE	100-44-7
11	BISPHENOL A DIGLYCIDYL ETHER	1675-54-3
12	BIUREA	110-21-4
13	1,3-BUTADIENE	106-99-0
14	2-BUTANONE PEROXIDE	1338-23-4
15	TERT-BUTYL PERBENZOATE	614-45-9
16	GAMMA-BUTYROLACTONE	96-48-0
17	CALCIUM CHROMATE	13765-19-0
18	CARBON DISULFIDE	75-15-0
19	CARBROMAL	77-65-6
20	CHLORAL HYDRATE	302-17-0
21	CHLORAMBEN	133-90-4
22	CHLORAMBUCIL	305-03-3
23	CHLORDANE (TECHNICAL GRADE)	12789-03-6
24	CHLORENDIC ACID	115-28-6
25	CHLORINATED TRISODIUM PHOSPHATE	56802-99-4
26	4-(CHLOROACETYL)ACETANILIDE	140-49-8
27	CHLOROBENZENE	108-90-7
28	2-CHLOROETHYLTRIMETHYLAMMONIUM CHLORIDE	999-81-5
29	3-CHLORO-2-METHYLPROPENE	563-47-3
30	CHLOROPRENE	126-99-8
31	CHLORPHENIRAMINE MALEATE	113-92-8
32	CHLORPROPAMIDE	94-20-2
33	CHROMIUM CARBONYL	13007-92-6
34	C.I. ACID RED 14	3567-69-9
35	COUMAPHOS	56-72-4
36	CYCLOPHOSPHAMIDE	50-18-0
37	CYCLOSPORIN A	59865-13-3
38	DECABROMODIPHENYL OXIDE	1163-19-5
39	DIARYLANILIDE YELLOW	6358-85-6
40	DIAZINON	333-41-5
41	1,2-DIBROMO-3-CHLOROPROPANE	96-12-8
42	1,2-DIBROMO-4-(1,2-DIBROMOETHYL)CYCLOHEXANE	3322-93-8
43	DIBROMOMANNITOL	488-41-5
44	DIBUTYLTIN DIACETATE	1067-33-0
45	DICHLOROACETONITRILE	3018-12-0
46	3,4-DICHLORONITROBENZENE	99-54-7

TABLE 8

CHEMICALS SELECTED TO BE TESTED FOR CYTOGENETIC EFFECTS IN CHINESE HAMSTER OVARY CELLS IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
47	2,4-DICHLORONITROBENZENE	611-06-3
48	2,3-DICHLORONITROBENZENE	3209-22-1
49	1,3-DICHLOROPROPENE (TELONE II)	542-75-6
50	DIELDRIN	60-57-1
51	DIETHANOLAMINE	111-42-2
52	1,8-DIHYDROXY-4,5-DINITROANTHRAQUINONE	81-55-0
53	2,4-DIMETHOXYANILINE HYDROCHLORIDE	54150-69-5
54	N,N-DIMETHYLANILINE	121-69-7
55	DIMETHYLFORMAMIDE	68-12-2
56	DIMETHYL TEREPHTHALATE	120-61-6
57	2,4-DINITROANILINE	97-02-9
58	2,7-DINITRO-9H-FLUOREN-9-ONE	31551-45-8
59	2,4-DINITROTOLUENE	121-14-2
60	DIPHENHYDRAMINE HYDROCHLORIDE	147-24-0
61	ENDRIN	72-20-8
62	1,2-EPOXYHEXADECANE	7320-37-8
63	1,2-EPOXY-3,3,3-TRICHLOROPROPANE	3083-23-6
64	ERYTHROMYCIN STEARATE	643-22-1
65	ETHYL BROMIDE	74-96-4
66	ETHYLENEDIAMINE TETRAACETIC ACID (EDTA)	150-38-9
67	ETHYLENE GLYCOL	107-21-1
68	ETHYLENE OXIDE	75-21-8
69	2-ETHYLHEXANOIC ACID	149-57-5
70	2-ETHYLHEXANOL	104-76-7
71	FERRIC AMMONIUM FERROCYANIDE	25869-00-5
72	FURAN	110-00-9
73	HC YELLOW 4	52551-67-4
74	HEXACHLOROBENZENE	118-74-1
75	HEXACHLOROCYCLOPENTADIENE	77-47-4
76	ISOPRENE	78-79-5
77	LASIOCARPINE	303-34-4
78	D-LIMONENE	5989-27-5
79	MALONALDEHYDE, SODIUM SALT	24382-04-5
80	2-MERCAPTOBENZIMIDAZOLE	583-39-1
81	ALPHA-METHYLBENZYL ALCOHOL	98-85-1
82	METHYLDOPA	555-30-6
83	NALIDIXIC ACID	389-08-2
84	NTA(NITRILOTRIACETIC ACID)	139-13-9
85	9-NITROANTHRACENE	602-60-8
86	4-NITROANTHRANILIC ACID	619-17-0
87	P-NITROBENZOYL CHLORIDE	122-04-3
88	3-NITRO-9-FLUORENONE	42135-22-8
89	NITROFURAZONE	59-87-0
90	P-NITROPHENOL	100-02-7
91	4-NITRO-O-PHENYLENEDIAMINE	99-56-9
92	1-PHENYL-3-METHYL-5-PYRAZOLONE	89-25-8

TABLE 8

CHEMICALS SELECTED TO BE TESTED FOR CYTOGENETIC EFFECTS IN CHINESE HAMSTER OVARY CELLS IN FY 1985

SEQ. NO.	CHEMICAL	CAS NO.
93	N-PHENYL-P-PHENYLENEDIAMINE	101-54-2
94	1-PHENYL-2-THIOUREA	103-85-5
95	PHOTODIELDRIN	13366-73-9
96	PHTHALAMIDE	88-96-0
97	PICRIC ACID	88-89-1
98	PROPYLENE OXIDE	75-56-9
99	1,3-PROPYLENE OXIDE	503-30-0
100	RHODAMINE 6G	989-38-8
101	ROTENONE	83-79-4
102	SODIUM CHLORIDE	7647-14-5
103	SODIUM DIETHYLDITHIOCARBAMATE	148-18-5
104	SODIUM DODECYL SULFATE	151-21-3
105	SUCCINIC ANHYDRIDE	108-30-5
106	3-SULFOLENE	77-79-2
107	2,3,5,6-TETRACHLORO-4-NITROANISOLE	2438-88-2
108	TETRACYCLINE HYDROCHLORIDE	64-75-5
109	TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM CHLORIDE	124-64-1
110	TITANIUM DIOXIDE	13463-67-7
111	TOLBUTAMIDE	64-77-7
112	TOLUENE (NITRATION GRADE)	108-88-3
113	TOLUENE (TECHNICAL)	108-88-3
114	2,5-TOLUENEDIAMINE SULFATE	6369-59-1
115	TRICHLORFON	52-68-6
116	2,4,5-TRIMETHOXYBENZALDEHYDE	4460-86-0
117	TRIMETHYLTHIOUREA	2489-77-2
118	TRIPHENYLTIN HYDROXIDE	76-87-9
119	4-VINYLCYCLOHEXENE	100-40-3
120	VINYLIDENE CHLORIDE (1,1-DICHLOROETHYLENE)	75-35-4
121	VINYLIDENE FLUORIDE	75-38-7
122	VINYL TOLUENE	25013-15-4

NCTR

UTILIZATION OF THE PRIMARY HEPATOCYTE/DNA REPAIR SYSTEM TO DETECT POTENTIAL GENOTOXICITY OF NTP CHEMICALS

Introduction -- It is known that DNA is the target for various cytotoxic, mutagenic, and carcinogenic chemicals, and is thought that a majority of chemical carcinogens or their metabolites are electrophiles that react with cellular nucleophiles such as nucleic acids and proteins. One result of nucleic acid binding is DNA repair. This is accomplished by excision of the adduct and subsequent polymerization and ligation of the DNA strand. One method for detecting DNA repair is the use of autoradiographic techniques to measure labeled thymidine incorporation into DNA of mammalian cells outside of the normal phase of DNA synthesis (unscheduled DNA synthesis, UDS). A variety of cell systems have been developed to detect UDS, ranging from rodent to human cells in culture, and these systems have been advocated for inclusion into a battery of assays to assess hazardous chemicals. The system used in this project is the primary hepatocyte/DNA repair system. The objective of this cooperative project with NIEHS/NTP is to test 40 coded NTP-selected chemicals in the primary hepatocyte/DNA repair system.

Experimental Design -- The standard protocol uses primary hepatocytes isolated following *in situ* perfusion of rat livers with collagenase. The hepatocytes are exposed for 18-24 hours at 37°C to a series of concentrations (dependent upon solubility) of the test chemical in medium containing ^{3}H-thymidine. The positive control, 2-AAF, is used to monitor the metabolic state of the hepatocyte preparation. Depending upon the nature of the chemical being evaluated, the negative control is the solvent used to dissolve the chemical and if the solvent is organic, e.g., DMSO, ethanol, or acetone, the final concentration will not exceed one percent. Dosage selection for the UDS assay is based on the solubility of the chemical and cytotoxic information obtained either from the NTP or based on preliminary cytotoxicity testing. A concentration that exhibits a cytotoxic response (or the highest soluble concentration, in the absence of cytotoxicity) is selected as the highest concentration for the UDS assay and the remaining four doses are selected over a 2-logarithm range.

The test agent is considered positive if the results demonstrate a concentration related, statistically significant increase in UDS over negative control values and/or a reproducible, statistically significant increase in UDS at one concentration. A negative conclusion is reached in the absence of a positive response, as defined above, when the test compound has been tested to cytotoxic levels or to the limits of solubility.

FY 1984 ACCOMPLISHMENTS

Forty chemicals have been received and solubility characteristics defined. Cells have been exposed to all of the chemicals. Twenty-four chemicals have been completely assessed while sixteen are still undergoing analysis. Of the twenty-four, two were clear-cut positives, three were considered questionable because of an increased percentage of cells in repair and are being re-analyzed, while nineteen were considered negative. The remaining 16 are at the grain counting stage and final evaluation is near completion. (CONTACT PERSON: Dr. D.A. Casciano).

FY 1985 PROGRAM PLANS

Forty coded chemicals will be evaluated in the standardized hepatocyte/DNA repair system.

NIOSH

The NIOSH program in cellular and genetic toxicology is directed to assessing genotoxic risks at the workplace. Potentially mutagenic airborne contaminants ranging from individual chemical substances to complex mixtures of chemicals may be present in certain occupational settings. Chemical manufacturing, coal gasification and liquefaction, underground mining using diesel equipment, and coke ovens are examples of industries and processes where workplace exposures are potentially hazardous. Many of these industries and processes produce mixtures containing hundreds of chemical compounds including polynuclear aromatic hydrocarbons, organic amines, and oxygenated and nitrated organic substances. To protect workers from potential mutagenic and associated risks, it is desirable to evaluate the presence of genotoxic substances at the worksite and to monitor employees for the presence of genotoxic substances or the occurrence of genotoxic events. By monitoring plant personnel and the workplace environment, heretofore unidentified genotoxic agents may be detected and proper procedures to safeguard workers from exposure to these industrial by-products could be adopted and would presumably benefit the health of workers and their offspring. Four projects aimed at assessing genotoxic risks to workers are in various stages of development and application.

FY 1984 ACCOMPLISHMENTS

Validation of the Arabinose Resistant Assay -- The arabinose resistant (Ara^r) assay system of Salmonella typhimurium with the tester strain developed in our laboratory was further validated with several azo dyes. Direct Black 38, Direct Red 2, and Direct Blue 15 were found to be mutagenic in the Ara^r assay system. This, and previously reported studies, indicate that this system is useful for detection of the mutagenic activity of chemical complexes and mixtures which are often present in the occupational setting. (CONTACT PERSON: Dr. T. Ong)

Methodology for Workplace Mutagenic Monitoring -- Studies on the establishment of assay methodologies for the in situ workplace mutagenic monitoring system have been completed. The trapping device consists of a pump, an impinger and a cyclone. An impinging air flow of 3 l/min generated by the pump is used. At this flow rate, both particles and vapors are effectively trapped. The impinger contains 20 ml of trapping medium and multi-drug resistant tester cells in a 100 ml glass flask and a fritted air bubbler. The cyclone can sufficiently remove non-respirable particles. In the control set, clean air is circulated among the cyclone, impinger, and pump by connecting the three apparatuses with tubings. For detecting promutagens, 5 ml of 9000 x g liver supernatant fraction (S9 mix) and 2.5 ml of tester cells are added to dialysis tubing which is immersed in the trapping medium. The results of laboratory studies with mutagen coated particles, vapors, gases, side-stream cigarette smoke and diesel emissions indicate that this system is potentially useful for monitoring mutagens in the workplace. (CONTACT PERSON: Dr. T. Ong)

Mutagenic Monitoring for High Risk Workers -- This project was cancelled. A new project may be initiated in the future if a suitable cohort can be selected for the study. (CONTACT PERSON: Dr. T. Ong)

Evaluation of Urine Mutagenesis Assay -- Studies have been conducted to determine whether the mutagens in fried beef, red wine and grape juice ingested by human subjects are excreted in the urine. Urine samples were collected from individuals before and after consumption of fried beef, wine or grape juice. The mutagenic activity of the collected samples was tested with the Ames Salmonella/microsome assay system. The results indicate that mutagenic activity was detected only in the samples collected from individuals after ingestion of fried beef. It seems that the mutagenic agents generated by the frying of beef are ingested, absorbed, and excreted by the human body in biologically detectable quantities. This study suggests that subjects should abstain from fried beef, but not wine or grape juice, at least one day prior to and during urine mutagenicity screening in the occupational setting. (CONTACT PERSON: Dr. T. Ong)

FY 1985 PROGRAM PLANS

Validation of the Arabinose Resistant Assay -- Validation of the Ara^r assay system will be continued in the laboratory using industrial chemicals, such as gases and volatile compounds. The mutagenic sensitivity of this system may be further evaluated with workplace chemicals and mixtures collected at the worksite. (CONTACT PERSON: Dr. T. Ong)

Methodology for Workplace Mutagenicity Monitoring -- Developments of the *in situ* mutagenic monitoring system to be continued in FY 1985 include: (1) sensitivity improvement, (2) further laboratory evaluation, and (3) field studies. (CONTACT PERSON: Dr. T. Ong)

Evaluation of Urine Mutagenesis Assay -- The longitudinal study initiated in FY 1984 will be continued. The mutagenic variability (if any) of urine samples collected from different human subjects and from the same subject at different times will be determined. (CONTACT PERSON: Dr. T. Ong)

In Vivo and Partial In Vivo Cytogenetic Studies -- Studies will be initiated in FY 1985 to treat mice with chemicals. Sister chromatid exchanges and chromosome aberrations in bone marrow cells and peripheral lymphocytes will be analyzed directly (*in vivo* - only for bone marrow cells) or after further culturing (partial *in vivo*). The information obtained could be useful for the evaluation of the reliability of cytogenetic studies to be used in the genetic monitoring of workers. (CONTACT PERSON: Dr. T. Ong)

CARCINOGENESIS RESEARCH AND TESTING

Despite advances in our understanding of cancer biology, and the development of more predictive short-term tests for genotoxic potential, the two-year exposure study in rodents remains the most definitive method for detecting chemical carcinogens. All recognized human carcinogens that have been studied adequately have also been shown to cause cancer in laboratory animals under appropriate experimental conditions; the identification of carcinogens in animals provides guidance as to potential chemical hazards in humans, exposure to which should be minimized as an aid to cancer prevention. Thus, the NTP accepts the concept that chemicals found to cause cancer in animals should be considered capable of causing cancer in humans.

To identify those potential chemical carcinogens of most importance to human health, the NTP evaluates large production volume chemicals with a high probability of human exposure. More specifically, test chemicals are chosen on the bases of the extent (and level) of human exposure, volume of production, nature of the use, availability of toxicologic data (or lack thereof), suspected biological activity (such as mutagenicity), and chemical structure. Although carcinogenic activity is a major endpoint, several ancillary studies are commonly included to more adequately define test chemical toxicities and their cause. Chemical disposition (absorption, distribution, metabolism, excretion), genetic toxicology, assessment of effects on fertility and reproduction, target organ characterization (especially in prechronic studies), immunotoxicity, and clinical pathology (e.g., clinical chemistries, hematology, urinalyses) are examples of studies performed in addition to the two-year chronic toxicology and carcinogenesis studies.

The "standard" two-year rodent carcinogenicity study, although modified extensively by the NTP, remains similar in structure to that developed by the NCI. A typical protocol employs both sexes of rats (usually the Fischer 344 hybrid strain) and mice (usually the $B6C3F_1$ hybrid strain), and administration of multiple doses (usually three, plus vehicle and/or untreated concurrent controls) of the test chemical to groups of at least 50 animals for approximately two years. The animals are generally 6-10 weeks of age at initiation of test chemical administration. Dose ranges for the chronic (usually two-year) study are based on estimates of maximum non-lethal, minimally toxic doses dose-response curves, pharmacokinetic considerations, probable levels of human exposure and other relevant factors. Generally, the lower doses are some set fraction of the highest dose. In addition to the two-year exposure groups, some animals are killed after 15 months of exposure to evaluate chronic toxicity before the onset of senescent changes.

As originally developed some years ago, the prechronic studies (generally 14-day and 90-day studies) were carried out principally to aid in dose selection for chronic carcinogenicity testing. However, the NTP has broadened the toxicological characterization, expanding the study to detect chemical toxicity. The prechronic toxicity studies, along with chemical disposition and genetic toxicity information, are used to better tailor the chronic study design to the chemicals being evaluated, as well as to provide relevant toxicologic information. Indeed, the prechronic and ancillary studies often identify target organ toxicity for further study. Such data are also used to determine the relative priority of candidate chemicals for chronic study, as well as the extent and level of detail of the study design.

The majority of the NTP prechronic and chronic studies are managed by the NIEHS component. In addition, some studies are conducted by the NCTR component and others by the NIOSH component. The NIOSH-managed studies generally involve substances and routes of administration associated with human occupational exposures.

NIEHS

FY 1984 ACCOMPLISHMENTS

TESTING - PRECHRONIC AND TWO-YEAR STUDIES

During FY 1984, 13 two-year studies were completed and the technical reports of the findings were approved by the ad hoc scientific peer review panel associated with the NTP Board of Scientific Counselors (Table 9). New categories adopted by the NTP in FY 1983 continue to be used in the Technical Reports to describe the strength of experimental evidence for each individual study result -- that is, for male rats, female rats, male mice, and female mice. Five categories were adopted to maintain consistency in defining evidence of carcinogenicity, and are:

- Clear Evidence of Carcinogenicity is demonstrated by studies that are interpreted as showing a chemically-related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit a substantially increased incidence of a combination of malignant and benign neoplasms where each increases with dose.

- Some Evidence of Carcinogenicity is demonstrated by studies that are interpreted as showing a chemically-related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.

- Equivocal Evidence of Carcinogenicity is demonstrated by studies that are interpreted as showing marginal increases of neoplasms.

- No Evidence of Carcinogenicity is demonstrated by studies that are interpreted as showing no chemically-related increases in malignant or benign neoplasms.

- Inadequate Study of Carcinogenicity demonstrates that because of major qualitative or quantitative limitations the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

These explanations are given in the Note to the Reader Section of each Technical Report.

Under the conditions of the studies and using the five categories, there were five (38%) where there was clear evidence of carcinogenicity in one or more of the sexes and/or species; there were three (23%) where there was some evidence of carcinogenicity in one or more of the sexes/species; there was one study (8%) considered equivocal; and there were four studies (31%) where there was no evidence of carcinogenicity (Table 9). Data audits were completed prior to peer review for all of these studies and no data discrepancies were found that influenced final interpretation. A summary audit report is included in the draft and final reports for all studies. When available, NTP Technical Reports may be obtained from the NTP Public Information Office, MD B2-04, P.O. Box 12233, Research Triangle Park, NC 27709.

Status of Testing -- There were 21 chemicals in the prechronic phase of toxicology and carcinogenesis testing (Table 10) and 169 chemicals in the chronic phase (normally two-year) (Table 11) at the end of FY 1984. Those in the chronic phase include studies that are in the histopathology and report preparation phases.

All prechronic and long-term toxicology and carcinogenesis studies are under direct NTP management, and most are performed through a master agreement contracting mechanism whereby laboratories and their personnel are qualified for standard protocols and in each of various special study areas prior to announcing requests for proposal (RFPs). This provides a pool of qualified laboratories to compete for awards to do studies on chemicals according to specific protocols.

The NTP protocols for conduct of acute, 14-day repeated dose, 90-day prechronic, and two-year chronic studies in rodents were again revised and updated to incorporate refinements in study design. This is an ongoing process.

Master agreement awards were made to eight laboratories during FY 1984. These laboratories were Battelle Columbus, Battelle Pacific Northwest, Bioassay Systems, EG and G Mason Research, Hazelton Laboratories of America (Virginia), Litton Bionetics, Microbiological Associates, and Southern Research Institute. These awards are for a period of five years provided performance is satisfactory. Additional awards are anticipated in FY 1985. (CONTACT PERSON: Dr. M. Vernon).

Auditing of Data from Long-Term Carcinogenesis Studies -- The data auditing process begun in June 1983 continued in FY 1984. Scheduling is made according to the following descending priority ranking: (1) studies on chemicals scheduled for peer review where Technical Reports have been or are being drafted; (2) studies for which Technical Reports were written and approved by the Peer Review Panel prior to the beginning of the audit process; and (3) stud-ies already published and selected by the NTP Executive Committee's Subcommittee on Data Audits. Additional information on the audits including a listing of all data audits completed through the end of FY 1984 is given in the section on Chemical Pathology (Table 17). A more complete description of the process is included in the section on Data Audits.

Other Long-Term Studies -- The synthetic rubber component 1,3-butadiene was found to cause cancer in mice at concentrations of 625 and 1250 ppm, which are near the range of the current threshold limit value (TLV) of 1000. Further studies are being undertaken to evaluate dose-response relationships and the cause(s) of this carcinogenic effect in mice (also see Butadiene Initiative, pp. 133 to 134). (CONTACT PERSON: Dr. R. Melnick)

Chronic toxicity and carcinogenicity studies of a polybrominated biphenyl mixture (Firemaster FF-1®), diphenylhydantoin (phenytoin) and ethylenethiourea are being conducted concurrently in animals treated during the post-weaning phase of life and those treated in utero (gestation), neonatally and post-weaning. The objective of these studies is to determine whether gestational and neonatal exposure to the test chemicals can alter susceptibility to chronic toxicologic and carcinogenic effects. (CONTACT PERSON: Dr. R. Chhabra)

TEST METHODS DEVELOPMENT AND VALIDATION

Long Term Animal Testing Methodology -- Information is given in the Data Management and Analysis Section.

Short-Term Carcinogenesis Assays -- Information is given in the Chemical Pathology Section.

FY 1985 PROGRAM PLANS

TESTING - PRECHRONIC AND TWO-YEAR STUDIES

For FY 1985, the NTP has scheduled 31 chemical starts in the prechronic phase of the toxicology and carcinogenesis testing process (Table 12), and 21 starts in the chronic phase (Table 13). It is projected that 21 two-year studies will be completed through the in-life phase of toxicity testing in FY 1985 (Table 14). (CONTACT PERSON: Dr. L. Hart)

Human Carcinogen Data Base -- There are approximately 25 chemicals for which convincing epidemiologic evidence exists linking exposure to the development of cancer in humans. These studied adequately in animals have also produced carcinogenic responses. Because several chemicals have not been examined in laboratory animals or were studied some time ago using less than adequate designs, however, this data base needs further study to better evaluate current methodologies for assessing carcinogenic potential. Therefore, NIEHS/NTP has begun a literature initiative to comparatively evaluate the available studies on these human carcinogens to determine which need long-term studies. The data generated will provide a basis for studying these chemicals in F344 rats and $B6C3F_1$ mice. (CONTACT PERSON: Dr. R. Irwin)

TABLE 9

NTP TOXICOLOGY AND CARCINOGENESIS STUDY RESULTS

CHEMICAL/CAS NTP NUMBER	NTP/TR REPORT NO. -- PEER REVIEW DATE	USE	ROUTE/DOSE	TESTING LABORATORY	NTP CHEMICAL MANAGER	RESULTS UNDER THE CONDITIONS OF THESE STUDIES
ASBESTOS, CHRYSOTILE 12001-29-5 11331-N	NTP-83-173 TR-295 07/27/84	IN CEMENT WATER PIPES, INSULATION, FILTERS IN BEER AND WINE INDUSTRY	1% IN DIET FOR LIFETIME	HAZLETON LABORATORIES AMERICA, INC.	DR. E. E. MCCONNELL	THERE WAS NO EVIDENCE OF CARCINOGENICITY IN MALE OR FEMALE RATS EXPOSED TO SR CHRYSOTILE OR IN FEMALE RATS EXPOSED TO IR CHRYSOTILE ASBESTOS. THERE WAS SOME EVIDENCE OF CARCINOGENICITY IN MALE RATS EXPOSED TO IR CHRYSOTILE ASBESTOS AS INDICATED BY AN INCREASED INCIDENCE OF ADENOMATOUS POLYPS IN THE LARGE INTESTINE. THE COCARCINOGENIC STUDIES OF 1,2-DIMETHYLHYDRAZINE DIHYDROCHLORIDE AND IR CHRYSOTILE ASBESTOS DID NOT INDICATE THAT IR CHRYSOTILE ASBESTOS HAD EITHER A TUMOR-ENHANCING OR PROTECTIVE EFFECT.
BENZENE 71-43-2 10389-Y	NTP-83-072 TR-289 07/27/84	IN GASOLINE. RAW MATERIAL FOR SYNTHESIS OF PLASTICS, RUBBER, DYES, TEXTILE,DRUGS, INSECTICIDES. SOLVENT	GAVAGE (CORN OIL) 5 TIMES/ WK: MALE RATS--0,50,100 OR 200 MG/KG; FEMALE RATS AND MICE--0,25,50 OR 100 MG/KG	BATTELLE COLUMBUS LABORATORIES	DR. J. E. HUFF	THERE WAS CLEAR EVIDENCE OF CARCINOGENICITY OF BENZENE FOR MALE AND FEMALE F344/N RATS AND FOR MALE AND FEMALE B6C3F1 MICE. FOR MALE RATS BENZENE CAUSED INCREASED INCIDENCES OF ZYMBAL GLAND CARCINOMAS,SQUAMOUS CELL PAPILLOMAS AND SQUAMOUS CELL CARCINOMAS OF THE ORAL CAVITY, AND SQUAMOUS CELL PAPILLOMAS AND CARCINOMAS OF THE SKIN. FOR FEMALE RATS BENZENE CAUSED INCREASED INCIDENCES OF ZYMBAL GLAND CARCINOMAS AND SQUAMOUS CELL PAPILLOMAS AND SQUAMOUS CELL CARCINOMAS OF THE ORAL CAVITY. FOR MALE MICE BENZENE CAUSED INCREASED INCIDENCES OF ZYMBAL GLAND SQUAMOUS CELL CARCINOMAS, MALIGNANT LYMPHOMAS, ALVEOLAR/BRONCHIOLAR CARCINOMAS, HARDERIAN GLAND ADENOMAS, AND SQUAMOUS CELL CARCINOMAS OF THE PREPUTIAL GLAND. FOR FEMALE MICE BENZENE CAUSED INCREASED INCIDENCES OF MALIGNANT LYMPHOMAS, OVARIAN GRANULOSA CELL TUMORS, OVARIAN BENIGN MIXED TUMORS, CARCINOMAS AND CARCINOSARCOMAS OF THE MAMMARY GLAND, ALVEOLAR/BRONCHIOLAR ADENOMAS, ALVEOLAR/BRONCHIOLAR CARCINOMAS, AND ZYMBAL GLAND SQUAMOUS CELL CARCINOMAS.

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TABLE 9 (CONTINUED)

CHEMICAL/CAS NTP NUMBER	NTP/TR REPORT NO. -- PEER REVIEW DATE	USE	ROUTE/DOSE	TESTING LABORATORY	NTP CHEMICAL MANAGER	RESULTS UNDER THE CONDITIONS OF THESE STUDIES
1,3-BUTADIENE 106-99-0 10514-J	NTP-83-071 TR-288 10/28/83	INTERMEDIATE IN THE PRODUCTION OF ELASTOMERS, POLYMERS, AND OTHER CHEMICALS	INHALATION: MICE: 0, 625 OR 1,250 PPM; 6 HOURS/DAY, 5 DAYS/WEEK	BATTELLE PACIFIC NORTHWEST LABS	DR. R. L. MELNICK	THERE WAS CLEAR EVIDENCE OF CARCINOGENICITY FOR 1,3-BUTADIENE IN MALE AND FEMALE B6C3F1 MICE, AS SHOWN BY INCREASED INCIDENCES AND EARLY INDUCTION OF HEMANGIOSARCOMAS OF THE HEART, MALIGNANT LYMPHOMAS, ALVEOLAR/BRONCHIOLAR ADENOMAS AND CARCINOMAS, AND PAPILLOMAS OF THE STOMACH IN MALES AND FEMALES, AND OF ACINAR CELL CARCINOMAS OF THE MAMMARY GLAND, GRANULOSA CELL TUMORS OF THE OVARY, AND HEPATOCELLULAR ADENOMAS AND ADENOMAS OR CARICNOMAS (COMBINED) IN FEMALES. 1,3-BUTADIENE WAS ASSOCIATED WITH NONNEOPLASTIC LESIONS IN THE RESPIRATORY EPITHELIUM, LIVER NECROSIS, AND TESTICULAR OR OVARIAN ATROPHY.
CHLORODIBROMOMETHANE 124-48-1 10570-R	NTP-83-065 TR-282 03/23/84	FORMED AFTER CHLORINATION OF DRINKING WATER SUPPLIES	GAVAGE (CORN OIL) 5 TIMES/ WEEK: RATS--0, 40 OR 80 MG/KG; MICE--0, 50 OR 100 MG/KG	EG&G MASON RESEARCH INSTITUTE	DR. J. K. DUNNICK	THERE WAS NO EVIDENCE OF CARCINOGENICITY IN MALE OR FEMALE F344/N RATS RECEIVING CHLORODIBROMOMETHANE. FATTY METAMORPHOSIS AND GROUND-GLASS CYTOPLASMIC CHANGES OF THE LIVER IN MALE AND FEMALE F344/N RATS WERE RELATED TO ADMINISTRATION OF CHLORODIBROMOMETHANE. THERE WAS EQUIVOCAL EVIDENCE OF CARCINOGENICITY FOR MALE B6C3F1 MICE. MALE MICE RECEIVING CHLORODIBROMOMETHANE SHOWED AN INCREASED INCIDENCE OF HEPATOCELLULAR CARCINOMAS, WHEREAS THE COMBINED INCIDENCE OF HEPATOCELLULAR ADENOMAS OR CARCINOMAS WAS ONLY MARGINALLY INCREASED. SOME EVIDENCE OF CARCINOGENICITY WAS OBSERVED FOR FEMALE B6C3F1 MICE, SINCE CHLORODIBROMOMETHANE CAUSED AN INCREASED INCIDENCE OF HEPATOCELLULAR ADENOMAS AND AN INCREASED COMBINED INCIDENCE OF HEPATOCELLULAR ADENOMAS OR CARCINOMAS.
2-CHLOROETHANOL 107-07-3 10517-W	NTP-83-028 TR-275 07/27/84	CHEMICAL INTERMEDIATE, SOLVENT, PLANT GROWTH STIMULATOR	DERMAL(ETHANOL /WATER) 5 DAYS /WEEK: RATS-- 0, 50 OR 100 MG/KG; MICE-- 0, 7.5 OR 15 MG/ANIMAL	LITTON BIONETICS INC.	DR. D. S. GOLDMAN	THERE WAS NO EVIDENCE OF CARCINOGENICITY OF 2-CHLOROETHANOL FOR MALE OR FEMALE F344/N RATS OR SWISS CD-1 MICE.

TABLE 9 (CONTINUED)

CHEMICAL/CAS NTP NUMBER	NTP/TR REPORT NO. -- PEER REVIEW DATE	USE	ROUTE/DOSE	TESTING LABORATORY	NTP CHEMICAL MANAGER	RESULTS UNDER THE CONDITIONS OF THESE STUDIES
DIALLYLPHTHALATE 131-17-9 10578-X	NTP-83-047 TR-284 03/23/84	CROSSLINKING AGENT FOR UNSATURATED POLYESTERS	GAVAGE (CORN OIL): RATS--0, 50 OR 100 MG/KG 5 TIMES/WEEK	LITTON BIONETICS, INC.	DR. W. M. KLUWE	THE ADMINISTRATION OF DIALLYLPHTHALATE BY GAVAGE IN CORN OIL TO MALE AND FEMALE F344/N RATS FOR 2 YEARS CAUSED CHRONIC LIVER DISEASE CHARACTERIZED BY PERIPORTAL FIBROSIS AND PIGMENT ACCUMULATION AND AN INCREASED SEVERITY OF BILE DUCT HYPERPLASIA. THE INCIDENCE OF MONONUCLEAR CELL LEUKEMIA WAS SIGNIFICANTLY INCREASED IN FEMALE RATS RECEIVING 100 MG/KG. BECAUSE OF THE VARIABILITY IN THE INCIDENCE OF THIS NEOPLASM IN AGED FISCHER 344 RATS AND THE DIFFICULTY IN DEFINITIVELY DIAGNOSING THIS LESION, THIS INCREASE WAS CONSIDERED TO BE EQUIVOCAL EVIDENCE OF CARCINOGENICITY OF DIALLYLPHTHALATE IN FEMALE RATS. THERE WAS NO EVIDENCE OF CARCINOGENICITY IN MALE RATS.
DIMETHYL HYDROGEN PHOSPHITE 868-85-9 10663-A	NTP-83-166 TR-287 07/27/84	INTERMEDIATE IN PRODUCTION OF INSECTICIDES & HERBICIDES; ADDITIVE TO LUBRICANTS; STABILIZER IN OIL & PLASTER	GAVAGE (CORN OIL) 5 TIMES/ WEEK: MICE AND MALE RATS--0, 100 OR 200 MG/ KG;FEMALE RATS-0, 50 OR 100 MG/KG	LITTON BIONETICS, INC.	DR. J. K. DUNNICK	THERE WAS CLEAR EVIDENCE OF CARCINOGENICITY IN MALE F344/N RATS RECEIVING DIMETHYL HYDROGEN PHOSPHITE, AS SHOWN BY INCREASED INCIDENCES OF ALVEOLAR/BRONCHIOLAR ADENOMAS, ALVEOLAR/BRONCHIOLAR CARCINOMAS, SQUAMOUS CELL CARCINOMAS OF THE LUNG, AND SQUAMOUS CELL PAPILLOMAS OR CARCINOMAS OF THE FORESTOMACH. THERE WAS EQUIVOCAL EVIDENCE OF CARCINOGENICITY IN FEMALE F344/N RATS RECEIVING DIMETHYL HYDROGEN PHOSPHITE, AS SHOWN BY MARGINALLY INCREASED INCIDENCES OF ALVEOLAR/ BRONCHIOLAR CARCINOMAS OF THE LUNG AND OF SQUAMOUS CELL NEOPLASMS OF THE FORESTOMACH. THERE WAS NO EVIDENCE OF CARCINOGENICITY FOR MALE OR FEMALE B6C3F1 MICE RECEIVING DIMETHYL HYDROGEN PHOSPHITE.
HAMAMELIS WATER (WITCH HAZEL WATER) 68916-39-2 10103-P	NTP-83-062 TR-286 03/23/84	USED IN COSMETICS	DERMAL (WATER) 0%, 50% OR 100%	GULF SOUTH RESEARCH INSTITUTE	DR. J. E. HUFF	THERE WAS NO EVIDENCE OF CARCINOGENICITY IN MALE OR FEMALE F344/N RATS OR IN MALE OR FEMALE B6C3F1 MICE THAT RECEIVED DERMAL APPLICATIONS OF HAMAMELIS WATER.

TABLE 9 (CONTINUED)

CHEMICAL/CAS NTP NUMBER	NTP/TR REPORT NO. -- PEER REVIEW DATE	USE	ROUTE/DOSE	TESTING LABORATORY	NTP CHEMICAL MANAGER	RESULTS UNDER THE CONDITIONS OF THESE STUDIES
H. C. BLUE NO. 1 2784-94-3 10715-Y	NTP-83-024 TR-271 03/23/84	SEMIPERMANENT HAIR DYE	FEED: RATS AND MALE MICE-- 0, 1,500 OR 3,000 PPM; FEMALE MICE--0, 3,000 OR 6,000 PPM	SOUTHERN RESEARCH INSTITUTE	DR. J. H. MENNEAR	THERE WAS EQUIVOCAL EVIDENCE OF CARCINOGENICITY IN MALE F344/N RATS RECEIVING HC BLUE NO. 1, AS INDICATED BY A MARGINAL INCREASE IN THE INCIDENCE OF HEPATOCELLULAR NEOPLASTIC NODULES/CARCINOMAS. FOR FEMALE F344/N RATS, THERE WAS SOME EVIDENCE OF CARCINOGENICITY IN THAT HC BLUE NO. 1 INDUCED INCREASES IN ALVEOLAR/BRONCHIOLAR ADENOMAS OR CARCINOMAS. THERE WAS CLEAR EVIDENCE OF CARCINOGENICITY OF HC BLUE NO. 1 FOR MALE AND FEMALE B6C3F1 MICE AS SHOWN BY INCREASED INCIDENCES OF HEPATOCELLULAR CARCINOMAS. FOLLICULAR CELL ADENOMAS OF THE THYROID GLAND WERE INCREASED IN MALE MICE.
H. C. BLUE NO. 2 33229-34-4 10788-R	NTP-83-170 TR-293 07/27/84	HAIR DYE	FEED: MALE RATS AND MICE--0, 5,000 OR 10,000 PPM; FEMALE RATS AND MICE--0, 10,000 OR 20,000 PPM	SOUTHERN RESEARCH INSTITUTE	DR. J. H. MENNEAR	THERE WAS NO EVIDENCE OF CARCINOGENICITY IN MALE OR FEMALE F344/N RATS OR IN MALE AND FEMALE B6C3F1 MICE RECEIVING HC BLUE NO. 2 IN THE DIET FOR 2 YEARS. HC BLUE NO. 2 CAUSED A DOSE-RELATED INCREASE IN THE INCIDENCE OF HYPEROSTOSIS OF THE SKULL IN MALE AND FEMALE RATS.
8-HYDROXYQUINOLINE 148-24-3 10590-N	NTP-83-029 TR-276 03/23/84	REAGENT, ANTIMICROBIAL, PRESERVATIVE, CHEMICAL INTERMEDIATE	FEED: RATS AND MICE--0, 1,500 OR 3,000 PPM	EG&G MASON RESEARCH INSTITUTE	DR. J. E. FRENCH	THERE WAS NO EVIDENCE OF CARCINOGENICITY FOR 8-HYDROXYQUINOLINE IN MALE OR FEMALE F344/N RATS OR IN MALE OR FEMALE B6C3F1 MICE.
TELONE II (R) (1,3-DICHLOROPROPENE) 542-75-6 10560-H	NTP-83-022 TR-269 07/27/84	SOIL FUMIGANT FOR PLANT PARASITIC NEMATODES	GAVAGE (CORN OIL): RATS--0, 25 OR 50 MG/KG; MICE--0, 50 OR 100 MG/KG 3 TIMES/WEEK	FREDERICK CANCER RESEARCH CENTER	DR. R. YANG	THERE WAS CLEAR EVIDENCE OF CARCINOGENICITY FOR MALE F344/N RATS, AS INDICATED BY A TELONE II(R)-RELATED INCREASED INCIDENCE OF SQUAMOUS CELL PAPILLOMAS AND CARCINOMAS OF THE FORESTOMACH, AS WELL AS AN INCREASED INCIDENCE OF NEOPLASTIC NODULES OF THE LIVER. IN FEMALE F344/N RATS, THERE WAS SOME EVIDENCE OF CARCINOGENICITY BECAUSE TELONE II(R) CAUSED AN INCREASED INCIDENCE OF SQUAMOUS CELL PAPILLOMAS OF THE FORESTOMACH. EVEN THOUGH THE EXPERIMENT IN MALE

(CONTINUED)

TABLE 9 (CONTINUED)

CHEMICAL/CAS NTP NUMBER	NTP/TR REPORT NO. -- PEER REVIEW DATE	USE	ROUTE/DOSE	TESTING LABORATORY	NTP CHEMICAL MANAGER	RESULTS UNDER THE CONDITIONS OF THESE STUDIES
TELONE II (R) (1,3-DICHLOROPROPENE) 542-75-6 10560-H	NTP-83-022 TR-269 07/27/84	SOIL FUMIGANT FOR PLANT PARASITIC NEMATODES	GAVAGE (CORN OIL): RATS--0, 25 OR 50 MG/KG; MICE--0, 50 OR 100 MG/KG 3 TIMES/WEEK	FREDERICK CANCER RESEARCH CENTER	DR. R. YANG	(TEXT CONTINUED) B6C3F1 MICE WAS CONSIDERED AN INADEQUATE STUDY OF CARCINOGENICITY BECAUSE OF REDUCED SURVIVAL IN THE VEHICLE CONTROL GROUP, THERE WAS SOME INDICATION THAT TELONE II(R) WAS ASSOCIATED WITH INCREASED INCIDENCES OF TRANSITIONAL CELL CARCINOMAS OF THE URINARY BLADDER, SQUAMOUS CELL PAPILLOMAS OF THE FORESTOMACH, AND ALVEOLAR/BRONCHIOLAR ADENOMAS AND CARCINOMAS OF THE LUNG. THERE WAS CLEAR EVIDENCE OF CARCINOGENICITY FOR FEMALE B6C3F1 MICE SINCE TELONE II(R) CAUSED INCREASED INCIDENCES OF TRANSITIONAL CELL CARCINOMAS OF THE URINARY BLADDER. TELONE II(R) ALSO INCREASED THE INCIDENCES OF ALVEOLAR/BRONCHIOLAR ADENOMAS OF THE LUNG AND OF SQUAMOUS CELL PAPILLOMAS OR CARCINOMAS OF THE FORESTOMACH IN THE FEMALE MICE. TELONE II(R)-RELATED NONNEOPLASTIC LESIONS INCLUDED BASAL CELL OR EPITHELIAL CELL HYPERPLASIA IN THE FORESTOMACH OF MALE AND FEMALE RATS AND MALE AND FEMALE MICE, AND EPITHELIAL HYPERPLASIA OF THE URINARY BLADDER IN MALE AND FEMALE MICE.
TRIS(2-ETHYLHEXYL) PHOSPHATE 78-42-2 10413-A	NTP-83-027 TR-274 P 10/28/83	VINYL PLASTIC AND SYNTHETIC RUBBER PLASTICIZER; CHEMICAL INTERMEDIATE; FLAME RETARDANT	GAVAGE (CORN OIL) 5 TIMES/WK MALE RATS--0, 2000 OR 4000 MG/KG;FEMALE RATS 0, 1000 OR 2000 MG/KG; MICE: 0, 500 OR 1000 MG/KG	LITTON BIONETICS INC.	DR. H. B. MATTHEWS	THERE WAS EQUIVOCAL EVIDENCE OF CARCINOGENICITY IN MALE F344/N RATS RECEIVING 2,000 AND 4,000 MG/KG TRIS(2-ETHYLHEXYL)PHOSPHATE, AS EVIDENCED BY INCREASED INCIDENCES OF PHEOCHROMOCYTOMAS OF THE ADRENAL GLANDS. THERE WAS NO EVIDENCE OF CARCINOGENICITY IN FEMALE F344/N RATS OR IN MALE B6C3F1 MICE RECEIVING TRIS(2-ETHYLHEXYL)PHOSPHATE. THERE WAS SOME EVIDENCE OF CARCINOGENICITY IN FEMALE B6C3F1 MICE THAT RECEIVED 1,000 MG/KG TRIS(2-ETHYLHEXYL)-PHOSPHATE, AS SHOWN BY AN INCREASED INCIDENCE OF HEPATOCELLULAR CARCINOMA. TRIS(2-ETHYLHEXYL)-PHOSPHATE WAS ASSOCIATED WITH INCREASED INCIDENCES OF FOLLICULAR CELL HYPERPLASIAS OF THE THYROID GLAND IN MALE AND FEMALE B6C3F1 MICE.

LEGENDS FOR TESTING TABLES
(Tables 10, 11, 12, 13, & 14)

CHEMICAL MANAGER CODES:

ABDK	- Dr. K. Abdo	NIEHS	KADF	- Dr. F. Kadlubar	NCTR
ALLW	- Dr. W. Allaben	NCTR	KLUW	- Dr. W. Kluwe	NIEHS
BIRL	- Dr. L. Birnbaum	NIEHS	LAMJ	- Dr. J. Lamb	NIEHS
BOOG	- Dr. G. Boorman	NIEHS	LEWT	- Dr. T. Lewis	NIOSH
BRID	- Dr. D. Bristol	NIEHS	LITN	- Dr. N. Littlefield	NCTR
BROS	- Dr. S. Brown	NIEHS	LOWL	- Dr. L. Lowry	NIOSH
BUCJ	- Dr. J. Bucher	NIEHS	LUSM	- Dr. M. Luster	NIEHS
CHAP	- Dr. P. Chan	NIEHS	MARR	- Dr. R. Maronpot	NIEHS
CHHR	- Dr. R. Chhabra	NIEHS	MATH	- Dr. H. Matthews	NIEHS
COLJ	- Dr. J. Collins	NIEHS	MCCE	- Dr. E. McConnell	NIEHS
CROG	- Mr. G. Cronin	NCTR	MELR	- Dr. R. Melnick	NIEHS
DANF	- Dr. F. Daniel	NIOSH	MENJ	- Dr. J. Mennear	NIEHS
DIEM	- Dr. M. Dieter	NIEHS	MONC	- Dr. C. Montgomery	NIEHS
DUNJ	- Dr. J. Dunnick	NIEHS	MOOW	- Dr. W. Moorman	NIOSH
EASW	- Dr. W. Eastin	NIEHS	NIER	- Dr. R. Niemeir	NIOSH
FREJ	- Dr. J. French	NIEHS	RAOG	- Dr. G. Rao	NIEHS
GOLJ	- Dr. J. Goldstein	NIEHS	RAUE	- Dr. E. Rauckman	NIEHS
GRED	- Dr. D. Greenman	NCTR	ROBD	- Dr. D. Roberts	NCTR
GUPB	- Dr. B. Gupta	NIEHS	ROYJ	- Dr. J. Roycroft	NIEHS
HALL	- Dr. L. Hall	NIEHS	SCHB	- Dr. B. Schwetz	NIEHS
HEAH	- Dr. H. Hearn	FCRC	THOM	- Dr. M. Thompson	NIEHS
HINJ	- Dr. J. Hinson	NCTR	VANE	- Dr. E. Van Stee	NIEHS
HUFJ	- Dr. J. Huff	NIEHS	WALD	- Dr. D. Walters	NIEHS
IOAM	- Dr. M. Ioannou	NIEHS	WHIC	- Dr. C. Whitmire	NIEHS
IRWR	- Dr. R. Irwin	NIEHS	WOLM	- Dr. M. Wolfe	NIEHS
JACC	- Dr. C. Jackson	NCTR	WOLG	- Dr. G. Wolff	NCTR
JAMW	- Dr. W. Jameson	NIEHS	YANR	- Dr. R. Yang	NIEHS

ROUTE - ROUTE OF ADMINISTRATION:

FEED - Orally with Food
GAV - Gavage
INHAL - Inhalation
SP - Skin Paint
WATER - Oral with Water

SPECIES:

M	- MICE	R	- RATS
H	- HAMSTERS		

TABLE 10

CHEMICALS IN THE PRECHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1984

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
1	9-AMINOACRIDINE HYDROCHLORIDE	134-50-9	RM	FEED	EASW
2	O-BENZYL-P-CHLOROPHENOL	120-32-1	M	SP	BIRL
3	BROMOBENZENE	108-86-1	RM	INHAL	KLUW
4	BROMOBENZENE	108-86-1	RM	GAV	KLUW
5	BUTYL BENZYL PHTHALATE	85-68-7	R	FEED	KLUW
6	1,8-CINEOL	470-82-6	RM	FEED	WOLG
7	CINNAMALDEHYDE	104-55-2	RM	FEED	WOLG
8	CODEINE	76-57-3	RM	FEED	DUNJ
9	DIETHYL PHTHALATE	84-66-2	RM	SP	KLUW
10	DIMETHYLOLDIHYDROXYETHYLENEUREA	1854-26-8	RM	INHAL	ROYJ
11	HEXACHLOROCYCLOPENTADIENE	77-47-4	RM	INHAL	ABDK
12	METHAPYRILENE	91-80-5	RM	FEED	JACC
13	PYRILAMINE	91-84-9	RM	FEED	ALLW
14	4,4-THIOBIS(6-TERT-BUTYL-M-CRESOL)	96-69-5	RM	FEED	BIRL
15	D-ALPHA-TOCOPHERYL ACETATE	58-95-7	RR	GAV	ABDK
16	TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDR	79-01-6	R	FEED	MELR
17	TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDR	79-01-6	R	GAV	MELR
18	TRIMELLITIC ANHYDRIDE	552-30-7	RM	FEED	CROG
19	TRIMELLITIC ANHYDRIDE	552-30-7	RM	GAV	CROG
20	TRIPROLIDINE	486-12-4	RM	FEED	CROG
21	TUNGSTEN CARBIDE	12070-12-1	RM	INHAL	

TABLE 11

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1984

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
1	ACETAMINOPHEN	103-90-2	RM	FEED	IRWR
2	ALLYL GLYCIDYL ETHER	106-92-3	RM	INHAL	BOOG
3	1-AMINO-2,4-DIBROMOANTHRAQUINONE	81-49-2	RM	FEED	HUFJ
4	2-AMINO-4-NITROPHENOL	99-57-0	RM	GAV	IRWR
5	2-AMINO-5-NITROPHENOL	121-88-0	RM	GAV	IRWR
6	AMPHETAMINE SULFATE	60-13-9	RM	FEED	DUNJ
7	AMPICILLIN TRIHYDRATE	7177-48-2	RM	GAV	GUPB
8	BENZALDEHYDE	100-52-7	RM	GAV	KLUW
9	BENZOFURAN	271-89-6	RM	GAV	IRWR
10	BENZYL ACETATE	140-11-4	RM	GAV	ABDK
11	BENZYL ALCOHOL	100-51-6	RM	GAV	DIEM
12	BORIC ACID	10043-35-3	M	FEED	DIEM
13	BROMODICHLOROMETHANE	75-27-4	RM	GAV	DUNJ
14	BROMOFORM	75-25-2	RM	GAV	MELR
15	2-BUTANONE PEROXIDE	1338-23-4	RM	SP	ABDK
16	TERT-BUTYL ALCOHOL	75-65-0	RM	WATER	MARR
17	N-BUTYL CHLORIDE *	109-69-3	RM	GAV	ROYJ
18	N-BUTYL CHLORIDE *	109-69-3	M	GAV	ROYJ
19	GAMMA-BUTYROLACTONE	96-48-0	RM	GAV	IRWR
20	D-CARVONE *	2244-16-8	RM	GAV	ROYJ

TABLE 11

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1984

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
21	D-CARVONE *	2244-16-8	R	GAV	ROYJ
22	CASTOR OIL	8001-79-4	RM	FEED	COLJ
23	CHLORAMINE	10599-90-3	RM	WATER	WHIC
24	CHLORENDIC ACID	115-28-6	RM	FEED	FREJ
25	CHLORINATED TRISODIUM PHOSPHATE	56802-99-4	MR	GAV	WHIC
26	MONOCHLOROACETIC ACID	79-11-8	RM	GAV	EASW
27	CHLOROACETOPHENONE (CN)	532-27-4	RM	INHAL	MELR
28	P-CHLOROANILINE	106-47-8	RM	GAV	CHHR
29	O-CHLOROBENZALMALONONITRILE (CS)	2698-41-1	RM	INHAL	ABDK
30	3-CHLORO-2-METHYLPROPENE	563-47-3	RM	GAV	CHAP
31	CHLOROWAX 40	51990-12-6	RM	GAV	BUCJ
32	CHLOROWAX 500C	63449-39-8	RM	GAV	BUCJ
33	CHLORPHENIRAMINE MALEATE	113-92-8	RM	GAV	MELR
34	C.I. ACID ORANGE 3	6373-74-6	RM	GAV	MENJ
35	C.I. ACID RED 114	6459-94-5	R	WATER	MENJ
36	C.I. BASIC RED 9	569-61-9	RM	FEED	EASW
37	C.I. DIRECT BLUE 15	2429-74-5	R	WATER	MENJ
38	C.I. DISPERSE BLUE 1	2475-45-8	RM	FEED	RAUE
39	C.I. PIGMENT RED 3	2425-85-6	RM	FEED	MENJ
40	C.I. PIGMENT RED 23	6471-49-4	RM	FEED	MENJ

TABLE 11

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1984

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
41	COCONUT DIETHANOLAMIDE	68603-42-9	RM	SP	MELR
42	COUMARIN	91-64-5	RM	GAV	THOM
43	DECABROMODIPHENYL OXIDE	1163-19-5	RM	FEED	MATH
44	2,4-DIAMINOPHENOL DIHYDROCHLORIDE	137-09-7	RM	GAV	IRWR
45	4,4'-DIAMINO-2,2'-STILBENEDISULFONIC ACI	81-11-8	RM	FEED	EASW
46	2,3-DIBROMO-1-PROPANOL	96-13-9	RM	SP	MELR
47	1,4-DICHLOROBENZENE (P-DICHLOROBENZENE)	106-46-7	RM	GAV	COLJ
48	DICHLOROMETHANE (METHYLENE CHLORIDE)	75-09-2	RM	INHAL	MENJ
49	2,4-DICHLOROPHENOL	120-83-2	RM	FEED	MELR
50	DICHLORVOS	62-73-7	RM	GAV	CHAP
51	DIESEL FUEL MARINE	DIESELFUEL	M	SP	DIEM
52	DIETHANOLAMINE	111-42-2	RM	GAV	MELR
53	DIMETHOXANE	828-00-2	RM	GAV	ABDK
54	3,3'-DIMETHOXYBENZIDINE	119-90-4	R	WATER	MENJ
55	N,N-DIMETHYLANILINE	121-69-7	RM	GAV	ABDK
56	3,3'-DIMETHYLBENZIDINE	119-93-7	R	WATER	MENJ
57	DIMETHYL METHYLPHOSPHONATE	756-79-6	RM	GAV	DUNJ
58	DIMETHYL MORPHOLINOPHOSPHORAMIDATE	597-25-1	RM	GAV	CHAP
59	DIMETHYLVINYL CHLORIDE *	513-37-1	RM	GAV	SCHB
60	DIMETHYLVINYL CHLORIDE *	513-37-1	M	GAV	SCHB

TABLE 11

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1984

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
61	DIPHENHYDRAMINE HYDROCHLORIDE	147-24-0	RM	FEED	MELR
62	DOXYLAMINE	469-21-6	RM	FEED	JACC
63	EPHEDRINE SULFATE	134-72-5	RM	FEED	IRWR
64	EPINEPHRINE HYDROCHLORIDE	55-31-2	RM	INHAL	ROYJ
65	1,2-EPOXYBUTANE	106-88-7	RM	INHAL	DUNJ
66	1,2-EPOXYHEXADECANE	7320-37-8	RM	SP	MELR
67	ERYTHROMYCIN STEARATE	643-22-1	RM	FEED	FREJ
68	2-ETHOXYETHANOL (EGMEE)	110-80-5	RM	GAV	MELR
69	ETHYL BROMIDE	74-96-4	RM	INHAL	VANE
70	ETHYL CHLORIDE	75-00-3	RM	INHAL	VANE
71	ETHYLENE GLYCOL	107-21-1	M	FEED	MELR
72	ETHYLENE OXIDE	75-21-8	M	INHAL	LEWT
73	ETHYLENE THIOUREA	96-45-7	RM	FEED	CHHR
74	FURAN	110-00-9	RM	GAV	IRWR
75	FURFURAL	98-01-1	RM	GAV	IRWR
76	FUROSEMIDE	54-31-9	RM	FEED	BUCJ
77	GENTIAN VIOLET	548-62-9	RM	FEED	LITN
78	GLUTARALDEHYDE	111-30-8	RM	SP	HUFJ
79	GLYCIDOL	556-52-5	RM	GAV	IRWR
80	GLYCOL (POLYSORBATE 80)	9005-65-6	RM	FEED	ABDK

TABLE 11

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1984

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
81	HC RED 3	2871-01-4	RM	GAV	MENJ
82	HC YELLOW 4	52551-67-4	RM	FEED	EASW
83	HEXACHLOROETHANE	67-72-1	R	GAV	EASW
84	HEXAMETHYL-P-ROSANILINE CHLORIDE	548-62-9	RM	FEED	LITN
85	HEXYLRESORCINOL	136-77-6	RM	GAV	DUNJ
86	HYDROCHLOROTHIAZIDE	58-93-5	RM	FEED	BUCJ
87	HYDROQUINONE	123-31-9	RM	GAV	BRID
88	IODINATED GLYCEROL	5634-39-9	RM	GAV	FREJ
89	ISOPHORONE	78-59-1	RM	GAV	BUCJ
90	LAURIC ACID DIETHANOLAMINE CONDENSATE	120-40-1	RM	SP	CHHR
91	D-LIMONENE	5989-27-5	RM	GAV	JAMW
92	MALONALDEHYDE	542-78-9	RM	GAV	
93	MANGANESE SULFATE	7785-87-7	RM	FEED	WALD
94	MERCAPTOBENZOTHIAZOLE	149-30-4	RM	GAV	DIEM
95	MERCURIC CHLORIDE	7487-94-7	RM	GAV	DIEM
96	8-METHOXYPSORALEN	298-81-7	R	GAV	DUNJ
97	ALPHA-METHYLBENZYL ALCOHOL	98-85-1	RM	GAV	DIEM
98	METHYL BROMIDE	74-83-9	M	INHAL	YANR
99	METHYL CARBAMATE	598-55-0	RM	GAV	CHAP
100	METHYLDOPA	555-30-6	RM	FEED	DUNJ

TABLE 11

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1984

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
101	METHYL METHACRYLATE	80-62-6	RM	INHAL	CHAP
102	N-METHYLOLACRYLAMIDE	924-42-5	RM	GAV	BUCJ
103	MIREX	2385-85-5	R	FEED	HUFJ
104	NALIDIXIC ACID	389-08-2	RM	FEED	FREJ
105	NAPHTHALENE	91-20-3	M	INHAL	BROS
106	NAVY FUELS JP-5	8008-20-6	M	SP	DIEM
107	P-NITROANILINE	100-01-6	M	GAV	CHHR
108	O-NITROANISOLE	91-23-6	RM	FEED	CHHR
109	NITROFURANTOIN	67-20-9	RM	FEED	KLUW
110	NITROFURAZONE	59-87-0	RM	FEED	KLUW
111	P-NITROPHENOL	100-02-7	M	SP	IRWR
112	OCHRATOXIN A	303-47-9	R	GAV	BOOG
113	OLEIC ACID DIETHANOLAMINE	13961-86-9	RM	SP	CHHR
114	OXYTETRACYCLINE HYDROCHLORIDE	2058-46-0	RM	FEED	ABDK
115	PENICILLIN VK	132-98-9	RM	GAV	DUNJ
116	PENTACHLOROANISOLE	1825-21-4	RM	GAV	BRID
117	PENTACHLORONITROBENZENE	82-68-8	M	FEED	DUNJ
118	PENTACHLOROPHENOL, DOWICIDE EC-7	87-86-5	M	FEED	GOLJ
119	PENTACHLOROPHENOL, TECHNICAL	87-86-5	M	FEED	GOLJ
120	PENTAERYTHRITOL TETRANITRATE	78-11-5	RM	FEED	BUCJ

TABLE 11

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1984

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
121	PHENYLBUTAZONE	50-33-9	RM	GAV	GUPB
122	PHENYLEPHRINE HYDROCHLORIDE	61-76-7	RM	FEED	BUCJ
123	N-PHENYL-2-NAPHTHYLAMINE	135-88-6	RM	FEED	ABDK
124	O-PHENYLPHENOL	90-43-7	M	SP	LUSM
125	PHENYTOIN (DIPHENYLHYDANTOIN)	57-41-0	RM	FEED	CHHR
126	POLYBROMINATED BIPHENYL MIXTURE (FIREMAS	67774-32-7	RM	FEED	CHHR
127	PROBENECID	57-66-9	RM	GAV	
128	PYRIDINE	110-86-1	RM	GAV	FREJ
129	QUERCETIN	117-39-5	R	FEED	DUNJ
130	RESORCINOL *	108-46-3	RM	GAV	IRWR
131	RESORCINOL *	108-46-3	R	GAV	IRWR
132	RHODAMINE 6G	989-38-8	RM	FEED	FREJ
133	ROTENONE	83-79-4	R	IP/IJ	ALLW
134	ROTENONE	83-79-4	RM	FEED	ABDK
135	ROXARSONE	121-19-7	RM	FEED	ABDK
136	SODIUM AZIDE	26628-22-8	R	GAV	ABDK
137	SODIUM DODECYL SULFATE	151-21-3	RM	FEED	IRWR
138	SODIUM FLUORIDE	7681-49-4	RM	WATER	BUCJ
139	SODIUM XYLENESULFONATE	1300-72-7	RM	FEED	IRWR
140	SUCCINIC ANHYDRIDE *	108-30-5	M	GAV	HELR

TABLE 11

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1984

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
141	SUCCINIC ANHYDRIDE *	108-30-5	R	GAV	MELR
142	SULFAMETHAZINE	57-68-1	RM	FEED	LITN
143	TALC	14807-96-6	RM	INHAL	BROS
144	TETRACHLOROETHYLENE	127-18-4	R	GAV	MENJ
145	TETRACHLOROETHYLENE	127-18-4	R	GAV	MENJ
146	TETRACHLOROETHYLENE	127-18-4	R	GAV	MENJ
147	TETRACHLOROETHYLENE	127-18-4	R	GAV	MENJ
148	TETRACHLOROETHYLENE	127-18-4	M	GAV	MENJ
149	TETRACHLOROETHYLENE	127-18-4	RM	INHAL	MENJ
150	TETRACYCLINE HYDROCHLORIDE	64-75-5	RM	FEED	ABDK
151	TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM CHLOR	124-64-1	RM	GAV	JANW
152	TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM SULFA	55566-30-8	RM	GAV	JANW
153	TETRANITROMETHANE	509-14-8	RM	INHAL	BUCJ
154	TITANOCENE DICHLORIDE	1271-19-8	R	GAV	DIEM
155	TOLUENE (NITRATION GRADE)	108-88-3	RM	INHAL	HUFJ
156	TRIAMTERENE	396-01-0	RM	FEED	WHIC
157	TRICHLORFON	52-68-6	RM	GAV	CHAP
158	1,1,1-TRICHLOROETHANE (METHYL CHLOROFORM	71-55-6	RM	GAV	BIRL
159	TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDR	79-01-6	R	GAV	MENJ
160	TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDR	79-01-6	R	GAV	MENJ

TABLE 11

CHEMICALS IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES AT THE END OF FY 1984

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
161	TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDR	79-01-6	R	GAV	MENJ
162	TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDR	79-01-6	R	GAV	MENJ
163	TRIS(2-CHLOROETHYL) PHOSPHATE	115-96-8	RM	GAV	MATH
164	TUMERIC, OLEORESIN (CURCUMIN)	8024-37-1	RM	FEED	FREJ
165	4-VINYLCYCLOHEXENE	100-40-3	RM	GAV	COLJ
166	VINYL CYCLOHEXENE DIEPOXIDE	106-87-6	RM	SP	CHHR
167	VINYL TOLUENE	25013-15-4	RM	INHAL	BOOG
168	WOLLASTONITE CALCIUM SILICATES	13983-17-0	R	INHAL	MCCE
169	XYLENES, COMMERCIAL MIXTURE	1330-20-7	RM	GAV	EASW

* COUNTED AS ONE STUDY

TABLE 12

CHEMICALS SCHEDULED TO START IN THE PRECHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES IN FY 1985**

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
1	AZODICARBONAMIDE	123-77-3	RM	INHAL	BIRL
2	BENZETHONIUM CHLORIDE	121-54-0	RM	SP	EASW
3	BENZONITRILE	100-47-0	RM	GAV	IRWR
4	BENZO(F)-QUINOLINE	85-02-9	RM	INHAL	FREJ
5	BENZYL ACETATE	140-11-4	RM	FEED	ABDK
6	1,3-BUTADIENE	106-99-0	R	INHAL	MELR
7	TERT-BUTYL PERBENZOATE	614-45-9	RM	ORAL	MATH
8	BUTYRALDEHYDE	123-72-8	RM	INHAL	FREJ
9	BUTYRALDEHYDE	123-72-8	RM	GAV	FREJ
10	CROTONALDEHYDE	4170-30-3	RM	INHAL	FREJ
11	CROTONALDEHYDE	4170-30-3	RM	GAV	FREJ
12	1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE (MO	147-47-7	RM	SP	FREJ
13	1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE (PO	26780-96-1	RM	SP	FREJ
14	HEXACHLORO-1,3-BUTADIENE	87-68-3	M	FEED	YANR
15	1,6-HEXANEDIAMINE	124-09-4	RM	ORAL	FREJ
16	2-HYDROXY-4-METHOXYBENZOPHENONE	131-57-7	RM	FEED	FREJ
17	2-HYDROXY-4-METHOXYBENZOPHENONE	131-57-7	RM	SP	FREJ
18	ISOPRENE	78-79-5	RM	INHAL	MELR
19	NICKEL OXIDE	1313-99-1	RM	INHAL	DUNJ
20	NICKEL SULFATE HEXAHYDRATE	10101-97-0	RM	INHAL	DUNJ

** Known chemicals as of 10/01/84. Others may be scheduled as protocols are finalized.

TABLE 12

CHEMICALS SCHEDULED TO START IN THE PRECHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES IN FY 1985**

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
21	NICKEL SUBSULFIDE	12035-72-2	RM	INHAL	DUNJ
22	SALICYLAZOSULFAPYRIDINE	599-79-1	RM	FEED	
23	SCOPOLAMINE HYDROBROMIDE	51-34-3	RM	GAV	RAUE
24	SCOPOLAMINE HYDROBROMIDE	51-34-3	RM	WATER	RAUE
25	TETRACHLOROPHTHALIC ANHYDRIDE	117-08-8	RM	FEED	KLUW
26	TETRAHYDROFURAN	109-99-0	RM	INHAL	CHHR
27	TRICRESYL PHOSPHATE	1330-78-5	RM	FEED	IRWR
28	TRICRESYL PHOSPHATE	1330-78-5	RM	GAV	IRWR
29	TRIETHANOLAMINE	102-71-6	RM	WATER	MELR
30	TRIETHANOLAMINE	102-71-6	RM	SP	MELR
31	TRIETHANOLAMINE	102-71-6	RM	INHAL	MELR

** Known chemicals as of 10/01/84. Others may be scheduled as protocols are finalized.

TABLE 13
CHEMICALS SCHEDULED TO START IN THE CHRONIC PHASE OF TOXICOLOGY AND CARCINOGENESIS STUDIES IN FY 1985**

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
1	O-BENZYL-P-CHLOROPHENOL	120-32-1	M	SP	BIRL
2	O-BENZYL-P-CHLOROPHENOL	120-32-1	RM	GAV	BIRL
3	1,3-BUTADIENE	106-99-0	M	INHAL	MELR
4	CHLORAMINE	10599-90-3	RM	WATER	WHIC
5	C. I. DIRECT BLUE 218	28407-37-6	RM	FEED	MENJ
6	3,4-DIHYDROCOUMARIN	119-84-6	RM	GAV	THOM
7	DIETHYL PHTHALATE	84-66-2	M	SP	KLUW
8	DMBA/TPA/BPO (7,12-DIMETHYLBENZ(A)ANTH	57-97-6	M	SP	EASW
9	DMBA/TPA/BPO (7,12-DIMETHYLBENZ(A)ANTH	57-97-6	M	SP	EASW
10	DMBA/TPA/BPO (7,12-DIMETHYLBENZ(A)ANTH	57-97-6	M	SP	EASW
11	DIMETHYL PHTHALATE	131-11-3	M	SP	KLUW
12	METHAPYRILENE	91-80-5	RM	FEED	JACC
13	MNNG/TPA/BPO (N-METHYL-N'-NITRO-N-NITR	70-25-7	M	SP	EASW
14	MNNG/TPA/BPO (N-METHYL-N'-NITRO-N-NITR	70-25-7	M	SP	EASW
15	MNNG/TPA/BPO (N-METHYL-N'-NITRO-N-NITR	70-25-7	M	SP	EASW
16	P-NITROPHENOL	100-02-7	M	SP	IRWR
17	PROMETHAZINE HYDROCHLORIDE	58-33-3	RM	GAV	LUSM
18	PYRILAMINE	91-84-9	RM	FEED	ALLW
19	SODIUM FLUORIDE	7681-49-4	RM	WATER	BUCJ
20	TRIPELENNAMINE	91-81-6	RM	FEED	JACC
21	TRIPROLIDINE	486-12-4	RM	FEED	CROG

** Known chemicals as of 10/01/84. Others may be scheduled as protocols are finalized

TABLE 14

CHEMICALS FOR WHICH TOXICOLOGY AND CARCINOGENESIS STUDIES WILL BE COMPLETED THROUGH IN-LIFE PHASE IN FY 1985***

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
1	ACETAMINOPHEN	103-90-2	RM	FEED	IRWR
2	1-AMINO-2,4-DIBROMOANTHRAQUINONE	81-49-2	RM	FEED	HUFJ
3	O-CHLOROBENZALMALONONITRILE (CS)	2698-41-1	RM	INHAL	ABDK
4	C.I. ACID RED 114	6459-94-5	R	WATER	MENJ
5	C.I. DIRECT BLUE 15	2429-74-5	R	WATER	MENJ
6	C.I. PIGMENT RED 3	2425-85-6	RM	FEED	MENJ
7	C.I. PIGMENT RED 23	6471-49-4	RM	FEED	MENJ
8	2,4-DIAMINOPHENOL DIHYDROCHLORIDE	137-09-7	RM	GAV	IRWR
9	4,4'-DIAMINO-2,2'-STILBENEDISULFONIC ACID	81-11-8	RM	FEED	EASW
10	3,3'-DIMETHOXYBENZIDINE	119-90-4	R	WATER	MENJ
11	ETHYLENE GLYCOL	107-21-1	M	FEED	MELR
12	ETHYLENE THIOUREA	96-45-7	RM	FEED	CHHR
13	HC YELLOW 4	52551-67-4	RM	FEED	EASW
14	MERCURIC CHLORIDE	7487-94-7	RM	GAV	DIEM
15	PHENYTOIN (DIPHENYLHYDANTOIN)	57-41-0	RM	FEED	CHHR
16	POLYBROMINATED BIPHENYL MIXTURE (FIREMA	67774-32-7	RM	FEED	CHHR
17	RESORCINOL	108-46-3	R	GAV	IRWR
18	SULFAMETHAZINE	57-68-1	RM	FEED	LITN
19	TITANOCENE DICHLORIDE	1271-19-8	R	GAV	DIEM
20	TOLUENE (NITRATION GRADE)	108-88-3	RM	INHAL	HUFJ

TABLE 14

CHEMICALS FOR WHICH TOXICOLOGY AND CARCINOGENESIS STUDIES WILL BE COMPLETED THROUGH IN-LIFE PHASE IN FY 1985***

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
21	WOLLASTONITE CALCIUM SILICATES	13983-17-0	R	INHAL	MCCE

*** CHEMICALS FOR WHICH TERMINAL SACRIFICE WILL BE COMPLETED IN FY 1985

DATA FOR THESE CHEMICALS TO BE REPORTED BY FREDERICK CANCER RESEARCH FACILITY:

SEQ NO.	CHEMICAL NAME	PRIMARY CAS NUMBER	SPECIES	ROUTE	CHEM MGR
1	BENZYL CHLORIDE	100-44-7	RM	GAV	
2	CYCLOHEXANONE	108-94-1	RM	WATER	
3	METHAPYRILENE	91-80-5	RM	FEED	
4	N-NITROSODIETHANOLAMINE	1116-54-7	RM	WATER	
5	STYRENE OXIDE	96-09-3	RM	GAV	

NCTR

FY 1984 ACCOMPLISHMENTS

TESTING - PRECHRONIC AND TWO-YEAR STUDIES

This program conducts toxicological evaluations on food additives, animal or human drugs, pesticides, or other chemicals of interest to FDA that were nominated to the NTP. In addition to testing, this program also attempts to determine structure/activity relationships for toxicological endpoints of structurally similar compounds. To this goal the NCTR is examining such relationships with five structurally similar antihistamines, namely doxylamine, tripelennamine, triprolidine, pyrilamine and methapyrilene. In addition to those studies one antihistamine study began its chronic testing phase in FY 1984), prechronic studies were concluded for the antihistamines pyrilamine, doxylamine, tripelennamine, thenyldiamine, methapyrilene, triprolidine, and the food additive caffeine. Furthermore, final reports were submitted for the insecticide, rotenone, and the animal food additive, gentian violet, (mouse study) and three manuscripts were published dealing with the metabolism of gentian violet. Methods development has progressed for microencapsulation of the food flavoring agents cinnamaldehyde and 1,8-cineole. The results and status of each study are described below.

Pyrilamine

90-Day Subchronic Studies -- Dose levels in feed were: Mice - 0, 375, 750, 1500, 3000 and 6000 ppm; Rats - 0, 750, 1500, 3000, 6000, and 12000 ppm (free amine). Clinical signs observed were rough hair, hunched posture, and skinny appearance in rats and alopecia in mice. One mouse in the 3000 ppm group and two in the 6000 ppm group died during the study. In female rats there was a decrease in mean terminal body weights (compared to controls) in the three highest dose groups (3000, 6000 and 12000 ppm) and in male rats in the two highest dose groups. In male mice there was a reduction in terminal body weights for the three highest dose groups and in female mice for the 3000 ppm group. Neither rats nor mice exhibited gross lesions at necropsy. In rats there was a dose-related production of diffuse parenchymal cell cytomegaly of the parotid gland and liver parenchymal cell fatty degeneration. Similar effects were seen in salivary glands of mice. A final report was submitted to the NTP. (CONTACT PERSON: Dr. W. T. Allaben)

Methapyrilene

90-Day Subchronic Studies -- Studies in which methapyrilene was administered in the feed to rats and mice which were maintained on acid drinking water were performed in addition to parallel studies with animals on normal drinking water. Lesions were observed in several organs including liver, kidney, parotid glands, ovaries, uterus, vagina, and mammary glands in rats and mice from both acid and normal drinking water groups. Final reports for 90-day studies in mice are in preparation and/or review. Since methapyrilene was shown to be a hepatocarcinogen in other studies, no standard chronic studies are planned, but the chemical will be used in a limited study as a positive control for other antihistamines. (CONTACT PERSON: Dr. C. D. Jackson)

Doxylamine

90-Day Subchronic Studies -- Subchronic studies in rats and mice were completed. Dose levels of 0, 80, 162, 325, 750 and 1500 ppm (mice) and 0, 162, 405, 1012, 2530, and 6325 ppm (rats) were administered in the feed. The results indicated fatty changes and cytomegaly in livers and morphological changes in parotid salivary glands of rats and cytomegaly and karyomegaly in the livers of mice. After review by the NTP Toxicology Design Committee, dose levels were chosen for chronic studies: Rats 0, 500, 1000, and 2000 ppm; Mice - 0, 190, 375, and 750 ppm. A final report has been submitted to NTP.

Chronic Studies -- Chronic studies were begun in both rats and mice in April 1984. (CONTACT PERSON: Dr. C. D. Jackson)

Tripelennamine

90-Day Subchronic Study -- A 90-day study in both rats and mice was completed. Dose levels in feed were: Rats - 0, 150, 300, 600, 1200, 2400 ppm; mice - 0, 300, 600, 1200, 2400, and 4800 ppm. Tripelennamine was more toxic in rats than in mice. Lesions were observed in the livers, lungs and parotid glands of rats and mice. The histopathology is currently being reviewed by the NTP Pathology Working Group. Following completion of their review, dose levels for the chronic study will be chosen. A final report has been submitted to the NTP.

Chronic Study -- Following completion of the histopathology review and review by the NTP Experimental Design Committee, the chronic studies in both rats and mice will be initiated. An estimated start date of February 1985 is anticipated. (CONTACT PERSON: Dr. C. D. Jackson)

Thenyldiamine

90-Day Subchronic Study -- Dose levels in feed were: Rats - 0, 125, 250, 500, 1000, and 2000 ppm; Mice - 0, 250, 500, 1000, 2000, and 4000 ppm. There was significant weight loss in rats and mice. No gross observations of chemically related pathologies were noted in rats. Hepatocellular cytomegaly and karyomegaly occurred primarily at the two highest doses in male mice. A final report has been submitted to the NTP. (No further action is anticipated). (CONTACT PERSON: Mr. G. M. Cronin)

Triprolidine

90-Day Subchronic Study -- Dose levels in feed were: Mice and Rats - 0, 250, 500, 1000, 2000 and 4000 ppm. A greater than 10% decrement in body weight was observed in male and female rats and in male and female mice. Fatty changes in the liver were observed in both male and female rats. No tissue changes were noted in mice. The final report is in review. (CONTACT PERSON: Mr. G. M. Cronin)

Caffeine

90-Day Subchronic Study -- Caffeine was administered in the drinking water to male and female rats and mice at dose levels of: Rats - 0, 188, 375, 750, 1500, and 3000 ppm; Mice -0, 94, 188, 375, 750, and 1500 ppm. In rats, there was little effect on weight gain although animals in the 3000 ppm group lost

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weight initially and never regained the differential. Final body weights of the 3000 ppm groups of both males and females were reduced greater than 10%. In mice, only the 375 ppm dose group of males exhibited greater than 10% reduction compared to controls. No significant clinical signs were observed in either rats or mice. No dose-related effects were observed in serum levels of hepatic enzymes. There were no significant gross lesions observed in either rats or mice. Microscopically there was a dose related effect in rats with higher dose groups exhibiting alterations in the parotid and submaxillary salivary glands. There were no treatment-related lesions in mice, though salivary gland parenchymal cells often had abundant stored secretory granules. The final report for these studies has been submitted to the NTP and the Pathology Working Group (PWG) has reviewed the pathology. No further testing is anticipated with this compound. (CONTACT PERSON: Dr. W. T. Allaben)

Rotenone

18-Month Study -- Female Wistar rats were injected intraperitoneally with doses of 0, 2.5 and 25 µmol/kg (72 animals in each group). The 25 µmol/kg dose was toxic so groups at 5.0 µmol/kg were added. Animals were injected five days a week for a period of eight weeks and monitored for an additional 16 months before sacrifice. Evaluation of gross and microscopic pathology data revealed no dose-related lesions. The final report has been submitted to the NTP and a manuscript was published. (CONTACT PERSON: Dr. W. T. Allaben)

Gentian Violet

90-Day Subchronic Study -- Dose levels in feed were: Rats and mice - 0, 250, 500, 1000, 1500, and 2000 ppm. There were no deaths. A dose response in reduction of body weight gains was found. Pathological lesions were noted in mice in the lymph nodes, Harderian glands, liver, lung, trachea and pituitary gland. A final report was submitted to the NTP.

Chronic Study - Mice -- Dose levels in feed were: 0, 100, 300, and 600 ppm. Sacrifices were performed at 12, 18, and 24 months. Mortality was dose related. Dose related effects in females were noted for hepatocellular carcinomas, Harderian gland adenomas, erythropoiesis of the spleen, atrophy of the ovaries, and reticulum cell sarcomas (Type A) of the urinary bladder, uterus, ovaries, and vagina. A technical report for this phase of the gentian violet program was completed in October 1983.

Chronic Study - Rats -- Dose levels in feed were: 0, 100, 300, and 600 ppm. Sacrifices were performed at 12, 18 and 24 months. The histopathological examinations are currently being performed.

Multigeneration Study - Rats -- Dose levels in feed were 0, 100, 300 and 600 ppm. The F1a generation was allocated to the chronic study. The F3a generation is currently undergoing extensive histopathological examination. A teratology examination was completed on the F3b generation, and a report is being compiled. (CONTACT PERSON: Dr. N. A. Littlefield).

Sulfamethazine

90-Day Subchronic Study -- Dose levels in feed were: Rats and mice - 0, 300, 600, 1200, 2400, and 3600 ppm. There were no deaths. A dose response was noted with respect to reduction of body weight gain. The mice exhibited no histopathological responses. The examinations on the rats revealed a dose related response in both males and females for thyroid hyperplasia. A final report is in preparation.

Chronic Study - Mice -- Dose levels in feed were: 0, 300, 600, 1200, 2400 and 4800 ppm. The 24-month (terminal) sacrifice was conducted in August 1984.

Chronic Study - Rats -- Dose levels in feed were: 0, 10, 40, 600, 1200, and 2400 ppm. The animals were allocated to the study from the Fla generation of the multigeneration study in November 1982. The 24-month (terminal) sacrifice was conducted in December 1984.

Multigeneration Study - Rats -- Dose levels in feed were: 0, 10, 40, 600, 1200, and 2400 ppm. The study was started in August 1982. The F3a generation is undergoing a histopathological examination and the mating for the F3b teratology examination was accomplished in April 1984. (CONTACT PERSON: Dr. N. A. Littlefield).

1,8-Cineole

Bioavailability and palatability studies of microencapsulated 1,8-cineole administered to mice and rats in the feed were completed. The data indicated no adverse effects on food consumption or body weight gain. The compound could be detected in the blood of rats. (CONTACT PERSON: Dr. G. Wolff).

Cinnamaldehyde

Specifications have been identified for the production of encapsulated cinnamaldehyde that will result in a satisfactory product for use in animal bioassays. (CONTACT PERSON: Mr. H. Thompson).

FY 1985 PROGRAM PLANS

TESTING PRECHRONIC AND TWO-YEAR STUDIES

Two-year bioassays will continue for doxylamine and begin for pyrilamine, triplennamine, and triprolidine. Histopathological examinations will be completed for the two-year bioassay of gentian violet (rats), sulfamethazine (mice) and for the multigeneration studies of gentian violet and sulfamethazine.

The NCTR plans to conduct 28-day repeated dose studies with encapsulated 1,8-cineole in feed using rats and mice. For comparison, twenty-eight-day repeated dose gavage studies with rats and mice with the chemical in trioctanoin are also planned. The dosed feed and gavage experiments will be run simultaneously. Thirteen-week subchronic and 104-week chronic studies with rats and mice using encapsulated cineole dosed feed will follow.

A new contractor is being sought to produce encapsulated cinnamaldehyde according to the new specifications. The product will be evaluated by chemical analysis. Bioavailability and palatability experiments will be performed using rats and mice.

NIOSH

TESTING -- LONG-TERM STUDIES WITH EMPHASIS ON OCCUPATIONAL CARCINOGENESIS

NIOSH research emphasizes the identification of occupational environments which may produce cancer and includes: (1) assessment of the carcinogenic potential of complex mixtures encountered by workers; (2) modification of carcinogenesis by known and potential promoters and cocarcinogens that may be part of the work environment such as dusts, irritants, heat and sunlight; and (3) evaluation of factors such as work practices, medications and personal habits which may influence carcinogenicity in the workplace. The intent is to identify needed epidemiology and elucidate the etiology of cancers in the workplace. Identification of carcinogens leads to their control in the workplace.

FY 1984 ACCOMPLISHMENTS

Dimethylformamide -- A report is available describing the in-life results of a twelve-month inhalation study with dimethylformamide (DMF) in rats and mice at exposure concentrations of 0, 250 and 500 ppm. The study was terminated after 12 months at the convenience of the government. The outcome of this study agrees with the reported hepatotoxicity of inhaled DMF in rats and mice. A histopathological evaluation of the terminally killed animals is being conducted by NIOSH. (CONTACT PERSON: Dr. T. Lewis)

Short Asbestos Fibers -- A manuscript has been accepted by the journal "Fundamental and Applied Toxicology." The results of the study show that inhalation exposures of male rats to ball milled chrysotile asbestos at a concentration of 1 mg/m^3 (with 99.4% of the fibers shorter than 5 micrometers in length), 7 hrs/day, 5 days/wk for 18 months is insufficient to produce pulmonary fibrosis or tumors within 24 months. (CONTACT PERSON: Mr. F. Platek)

Dichlorethane: Drug Interactions -- This study is designed to study the toxic effects in rats of inhaled 1,2-dichloroethane (EDC) with concomitant administration of disulfiram in the diet or ethanol in the drinking water. The research, under contract to Midwest Research Institute, extends the previous findings with 1,2-dibromoethane to determine if the interaction between 1,2-dibromoethane and disulfiram has broader implications. During FY 1984, it was observed that mortality was not significantly different among the experimental groups, and because of the good survival at 18 months, the treatment period was extended to 24 months. Also added to the project was a study of EDC metabolism and DNA-specific binding. (CONTACT PERSON: Mr. K. Cheever)

Pyrolysis Effluents from Foundry Molds -- The experimental phase of a study to compare the carcinogenic potential of respirable particulate and water soluble effluents from four common types of molds -- "green sand," "shell," urethane, and furan -- used in iron casting operations was completed. The effluents generated immediately following pouring operations were collected and characterized chemically. Sampling procedures and analytical results have been published in trade and scientific journals. Preliminary findings of the bioassay will be published in the Proceedings of a NCI, EPA, NIOSH collaborative workshop on experimental carcinogenesis. The carcinogenic responses have been analyzed statistically, and found to be minimal, although hyperplasia was exaggerated. There are considerable differences apparent in the acute and chronic toxicity of the four effluents which will provide useful information for process substitution to provide a safer work environment in the foundry industry. (CONTACT PERSON: Mr. W. Moorman)

Foundry Mold Aggregates -- The purpose of this investigation was to assess chronic toxicity, cocarcinogenicity, and fibrogenicity of silica sand and several of its substitutes, including olivine, chromite sand, zirconium silicates, and aluminum silicates, when administered intratracheally to hamsters. Min-U-Sil was used as a reference quartz, ferric oxide as a positive cocarcinogen, and benzo(a)pyrene [B(a)P] as a carcinogen. No lung tumors were found in the saline control and very few were found in the absence of B(a)P -- ferric oxide, 1/41; Min-U-Sil, 1/50; zircon, 2/42; aluminum-70, 1/49. Except for aluminum-60, corrected tumor incidences were significantly greater than the saline-B(a)P group and similar to the ferric oxide-B(a)P positive control. It can be concluded from this study that: (1) neither of the crystalline quartz materials were carcinogenic in the hamster model; (2) silica sand and almost all substitute aggregates used in foundry mold production were cocarcinogenic; (3) the hamster is a poor model for studying fibrotic potential; and (4) granulomatous inflammation does not influence tumor development in the hamster. (CONTACT PERSON: Dr. R. Niemeier)

Acid Black 52 -- Carcinogenicity of Acid Black 52 administered to hamsters and rats in the diet (2%) and by intratracheal administration (hamsters 0.75 mg, rats 0.32 mg once weekly for 15 weeks) was studied. Definitive oncogenicity was not found in any case. Dietary administration suppressed the incidences of lymphoma/leukemia in bone marrow of hamsters and in the hematopoietic/lymphatic system, liver and lungs of rats. (CONTACT PERSON: Dr. T. Lewis)

Disperse Yellow 3 -- Carcinogenicity of Disperse Yellow 3 administered to hamsters and rats in the diet (0.8%) and by intratracheal administration (15.0 mg, once weekly for 15 weeks) was studied. Intratracheal administration resulted in increased incidences of carcinogenicity for the adrenal cortex of hamsters and pancreas of rats. Dietary administration demonstrated increased incidences of carcinogenicity for the adrenals of hamsters and for the liver and urinary tract of male rats. The incidences of lymphoma/leukemia in rats and hamsters were suppressed by dietary administration. (CONTACT PERSON: Dr. T. Lewis)

Silica -- Novaculite, a microcrystalline silica, produced adenocarcinomas following a single 20 mg dose given by intratracheal installation to 85 male Fischer 344 rats. Between and including the 12-and 22-month (final) observations, 21 of the 74 rats autopsied had lung tumors, primarily adenocarcinomas. This information was presented at a symposium on silica, silicosis and cancer in Chapel Hill, N.C. in April 1984. (CONTACT PERSON: Dr. L. Stettler)

Min-U-Sil -- The carcinogenicity of this crystalline quartz material for Fischer 344 rats previously reported by Holland et al. (Health Issues Related to Metal and Nonmetal Mining, Boston, Butterworth Publishers, 1983, pp. 485-496) was confirmed in an experiment where a single 2[illegible] mg dose of Min-U-Sil was given by intra-tracheal instillation to 85 male Fischer 344 rats. Between and including the 12-and 22-month (final) observations, 30 of 67 rats autopsied had lung tumors, all of which were adenocarcinomas. (CONTACT PERSON: Dr. L. Stettler)

Machine Oils and Nitrosamines -- This study was designed to study the carcinogenic potentials and promoter characteristics of synthetic machine cutting fluids following topical application of the undiluted materials to the shaven interscapular area of Agouti C3H/HeJ mice. Results of this study are not definitive, but suggest that some synthetic cutting fluids have potential for carcinogenicity to the liver of mice. A manuscript will be prepared comparing these data to other data in the literature involving mammalian carcinogenesis assessments of various nitrosamines. (CONTACT PERSON: Dr. R. Niemeier)

Roofing Asphalt and Coal Tar Pitch Fumes -- This study was designed to study the carcinogenicity of topically applied condensed asphalt and coal tar pitch fumes generated at recommended and commonly used (hotter) application temperatures. Two commercial types of asphalt and two types of coal tar pitch were studied. Two strains of male mice (CD-1 and C3H/HeJ) were used. The same experimental design was used with and without exposure of the mice to simulated sunlight immediately after application of the test material. Aliphatic hydrocarbons were major components of the petroleum asphalt fumes, while aromatic compounds were the major components of the coal tar pitch fumes. Fumes generated at the hotter than recommended application temperatures were more active than those generated at the recommended temperature. The Agouti C3H/HeJ mice were much more sensitive to carcinogenic activity of the fumes than the white CD-1 mice. The simulated sun light had an inhibitory effect on carcinogenesis. The activity of the coal tar pitch fumes reflected their B(a)P content. The asphalt fumes were more carcinogenic than expected, based on their B(a)P content. (CONTACT PERSON: Dr. R. Niemeier)

Asphalt Fumes -- Research was initiated to study the etiology of asphalt fume carcinogenesis. Asphalt fumes generated at 316°C have been collected, and are being fractionated into various major chemical classes. Skin painting studies will assess the initiating, cocarcinogenic, and promoting potentials of the fumes, their major components and various recombinations. The major objective is to determine an indicator that can be used to measure risks of asphalt fume exposure. (CONTACT PERSON: Dr. R. Niemeier)

TEST METHODS DEVELOPMENT AND VALIDATION

Short-Term Carcinogenicity Assays -- The experimental phase was completed of a study to compare the results among three contract laboratories on 25 coded chemicals tested in the V-79 metabolic cooperation system. Both promoters and cocarcinogens were evaluated. One laboratory did not complete all 25 chemicals because the principal investigator left. The data have not yet been analyzed to determine the components of variance, repeatability and other operating characteristics of the test. However, some problems were apparent with the test and it was planned to award two contracts in September 1984 to study the effects of varying: (1) time of adding 6-thioguanine; (2) calcium chloride concentration; and, (3) pH of the medium. Methods for employing neonatal epidermal cells in culture from three mouse strains to investigate early markers of tumor promotion/carcinogenesis continue to be developed. (CONTACT PERSON: Dr. J. Bohrman)

FY 1985 PROGRAM PLANS

A new bioassay of dimethylformamide will be designed based on experiences of the previous study. Commercially modified asbestos fibers will be assessed for carcinogenic potential using the intrapleural technique of Stanton. The contractor's final report on dichlorethane-drug interactions will be received and a manuscript prepared for publication. Manuscripts will be prepared describing the results of the biossays on Acid Black 52, Disperse Yellow 3, pyrolysis effluents from foundry molds, machine oils and nitrosamines, and the results of the interlaboratory study on the V-79 metabolic cooperation assay. Pending funding by interagency agreement, requests for contract proposals will be developed to study bladder cancer in animals, arsenic induced skin cancer, biological monitoring of workers exposed to aromatic amines, and to conduct an animal bioassay of vanadium pentoxide.

TOXICOLOGIC CHARACTERIZATION

Most chemicals selected for NTP testing are chosen because the potential exists for human exposure and little is known about their toxicologic profile. The toxicologic characterization program attempts to define two principal areas: (1) general toxicology which identifies the toxicity of a chemical by species, sex, dose, and essential organ function; and (2) specific toxicologic effects on the immunological, neurobehavioral, pulmonary, reproductive, and other systems.

The testing activities of the NTP toxicologic characterization program are composed primarily of 14-day, and 90-180 day experiments. These studies are often conducted as part of the prechronic testing phase of studies described in the Carcinogenesis Research and Testing section. Most chemicals selected for chronic (two-year) testing are evaluated in a group of genetic toxicity assays to determine potential for inducing gene mutations, chromosome damage, germ cell effects, DNA damage and repair, and cellular transformation, as well as to provide dose-response information. Many are also studied to delineate chemical disposition (absorption, metabolism, distribution, and excretion) patterns in order to improve the scientific knowledge base and the reliability and precision of dose setting for chronic studies. Also, comparative chemical disposition data by multiple routes of exposure are used to determine appropriate routes of exposure for toxicity testing. Information is routinely gathered, especially in prechronic studies, related to target organ effects, fertility and reproduction, urinalysis, clinical chemistry and hematology. Morphological assessment -- including tumor pathology, toxicologic pathology, experimental pathology and histology, and electron microscopy -- is an essential component of the toxicologic characterization.

Research activities in toxicologic characterization are concerned primarily with development and validation of improved test methods, and with more in-depth characterization and understanding the mechanisms of the toxic effects identified in the various testing phases (or by others). Specific disciplines and target organ areas include: biochemical toxicology and renal toxicology (described in this section), chemical disposition, chemical pathology, cutaneous toxicology, immunological toxicology, neurobehavioral toxicology and pulmonary toxicology (described in following sections).

NIEHS

FY 1984 ACCOMPLISHMENTS

General Toxicology

Broadened protocols now in use include measurement of organ weights, more extensive pathology in prechronic experiments, hematology, selected organ function assessment (including liver, kidney, immunologic, reproductive, and neurobehavioral effects), and chemical disposition. The general toxicology screen continues to include efforts to develop and evaluate clinical chemistry procedures for organ function assessment, as well as measures of reproductive function at the end of the 90-day prechronic phase -- testicular morphology, epididymal weights, sperm counts and morphology in male animals, and vaginal cytology in female animals. Efforts continue to develop toxicity principles for certain chemical classes, especially chlorinated aliphatic hydrocarbons, psoralens, phthalates and benzidine derivatives.

The evaluation of the subchronic (90-180 day) study results is a major decision point in the NTP. Results from the 14-day and 90-day studies, along with other information, may indicate that the standard experimental design should be modified, or that detailed special studies (e.g., reproductive toxicology), which would be done separately, are necessary to validate a presumptive toxic effect and to better characterize the toxic potential of the particular chemical. Examples of areas that could be included in special studies are: metabolism, clinical chemistry, hematology and urinalysis, pharmacokinetics, neurobehavioral toxicology, organ function, immunology, and endocrinology. (These special studies may be integrated into the prechronic or chronic testing phases.) The purpose of the special studies varies. They may focus on target organ toxicity, or on problems of comparative toxicology, metabolism, pathology, or physiology which would strengthen the ability to evaluate the animal model selected for the two-year toxicity and carcinogenicity study. In addition, a reanalysis is made at this time of the need for a chronic study. (CONTACT PERSON: Dr. W. Kluwe)

1,2-Dibromo-3-chloropropane -- The nematocide 1,2-dibromo-3-chloropropane (DBCP) causes immediate infertility in rats. A concommitant inhibition of sperm energy metabolism was found to occur. This effect of DBCP can be reproduced in vitro with isolated cauda epididymal sperm, suggesting that transport (and/or accumulation) of the pesticide to the epididymal fluid can impair fertility. (CONTACT PERSON: Dr. W. Kluwe)

Toxicity of Vitamin E Acetate (d-α-Tocopheryl Acetate) -- The biochemical and toxicological effects of mega doses (up to 2000 mg/kg) of Vitamin E administered by gavage are being investigated in male and female rats of two strains. (These studies are being done in collaboration with the FDA.) The in-life portion of the Sprague-Dawley rat study is complete and that of the Fischer 344 rats was completed in September 1984. Results from these studies will be reported shortly after completion of histological evaluations of the various tissues. (CONTACT PERSON: Dr. K. Abdo)

FY 1985 PROGRAM PLANS

Toxicity of Vitamin E Acetate (d-α-Tocopheryl Acetate) -- Because of the use of Vitamin E supplements in total parenteral nutrition therapy, particularly its use in the care of low-birthweight infants, and reports of deaths in premature infants receiving intravenous injections of Vitamin E preparations, additional animal studies are being considered. Among these is the study of the effects of various forms of Vitamin E (Vitamin E acetate, Vitamin E alcohol) administered intravenously to nursing pups or to pregnant dams. (CONTACT PERSON: Dr. K. Abdo)

Influence of Dietary Restriction on the Prevalance of Neoplastic and Non-Neoplastic Lesions and Reproduction -- The influence of moderate to severe dietary restriction on background tumor rate, prevalence of nutritionally related non-neoplastic lesions and reproduction in Fischer 344 rats and $B6C3F_1$ mice will be investigated. In addition, the effects of aging and dietary restriction on liver enzymes and liver mediated chemical mutagenicity in F344 rats will be studied.

Histopathological evaluations will be made on tissues of rats and mice of each dietary regimen at 3, 9, 15, 24, and 36 months from date of study initiation. Clinical chemistry determinations will be conducted at 3, 9, and 15 months. Mating trials will be conducted with male and female rats and with male and female mice subjected to dietary restriction for 3, 9, or 15 month periods. (CONTACT PERSON: Dr. K. Abdo)

Renal Toxicology

The kidney is a common target organ for chemical toxicants, due in part to its high rate of perfusion and its role as an excretory organ. Although the mammalian kidney has a remarkable ability to recover from acute insult, chronic renal disease is a common occurrence in prolonged-exposure toxicity studies and is a frequent factor in premature death. There is an urgent need, therefore, to detect nephrotoxic effects of chemicals and to define pathophysiological mechanisms of chemical nephropathies.

Mechanisms of acute and chronic chemical nephrotoxicity are being studied using both *in vivo* and *in vitro* techniques. Emphasis is placed on characterizing the functional impairments produced by nephrotoxicants, and their pathophysiologic basis. Dose-response is evaluated carefully to determine risks at various exposure levels, and chronicity is studied to assess the potential for cumulative toxicity. Of great interest is the differential response of various strains and species of animals to nephrotoxic chemicals.

The major objective of this initiative is to provide information which will aid in predicting the response of the human kidney to chemical exposure, thereby contributing to human health protection.

FY 1984 ACCOMPLISHMENTS

Retrospective Analysis -- A review of all chronic studies conducted by the NCI or the NTP revealed that approximately one-fourth of all chemicals studied caused chronic renal disease. By far the most common nephrotoxic classes were amines (especially aromatics) and halogenated hydrocarbons (especially short-chain aliphatics). Halogenated aliphatic compounds also tended to cause renal neoplasia (especially in male rats) while aromatic amines caused bladder tumors. (CONTACT PERSON: Dr. W. Kluwe)

Organohalide Nephrotoxicities -- A study was undertaken with hexachloro-1,3-butadiene, a very specific nephrotoxicant in rats, to evaluate early subcellular targets of organohalide nephrotoxicants. The earliest subcellular target in the kidney was endoplasmic reticulum, enzymatic activities of which were inhibited two hours after exposure. The nature of the endoplasmic reticulum effect is being explored. (CONTACT PERSON: Dr. W. Kluwe)

FY 1985 PROGRAM PLANS

Organohalide Nephrotoxicities -- *In vitro* techniques will be developed for identifying nephrotoxicants and for studying mechanisms of nephrotoxicity. The cause(s) and consequence of chemically-induced renal cytomegaly and karyomegaly will also be studied. (CONTACT PERSON: Dr. W. Kluwe)

Chemical Induction Of Fischer 344 Rat Mononuclear Cell Leukemia

NTP chronic toxicity test results indicate a high incidence of rat mononuclear cell leukemia (MNCL) in both control and treated F344 rats. It is difficult to determine if chemical induction of MNCL has occurred in a chronic test because of the high incidence of spontaneous MNCL. Responses to chemical treatment have included a statistically significant increase or decrease in MNCL as well as positive or negative trends with respect to dose. For example, there have been chemically related increased incidences of MNCL in NTP chronic tests of: Aroclor 1254, diazinon, phenol, piperonyl butoxide, and sulfisoxazole. There have also been increased MNCL incidences in at least one sex for: 2-amino-5-nitrothiazole, 3,3'-dimethoxybenzidine-4,4'-diisocyanate, lasiocarpine, 2,4,6-trichlorophenol and pyridine. There have been decreased MNCL incidences in chronic tests of: C.I. Disperse Yellow 3, D and C Red 9, C.I. Solvent Yellow 14, C.I. Acid Orange 10, 2-biphenylamine, propyl gallate, 11-aminoundecanoic acid, monuron, and monoethyl glycol ether.

Haseman (Fund. Appl. Toxicol., 3: 1-9, 1983) indicated that in 25 recent chronic dosed-feed studies in Fischer 344 rats, no chemically related lesions or positive trends were associated with leukemia/lymphoma. However, 9 out of 25 of these studies indicated a negative trend for leukemia/lymphoma. An interesting finding was the association of a negative trend for leukemia and lymphoma and a positive trend for liver tumors. Haseman also reported that in tests with liver tumor negative trends, a decrease in weight gain was associated with an increase in leukemia/lymphoma.

The occurrence and origin of Fischer 344 rat MNCL is not understood and inadequately studied. Therefore, our long-range goals are to: (1) develop a basis for understanding the effect of spontaneous leukemia incidence in the F344 rat and associated pathophysiology on the analysis and interpretation of NTP chronic toxicity tests; and (2) investigate chemical toxicity to the hematopoietic system in rats and chemical leukemogenesis.

Approach -- It is important to emphasize here the difference between chemically induced leukemias with their cytogenetic variability and the clonally derived rat leukemias that have been defined and possess reproducible characteristics of growth in culture and *in vivo* passage. The Long Evans, Brown Norway and BD IX rats have been described as having a low incidence of spontaneous leukemia. In contrast, the F344 rat affords the unique opportunity to investigate a spontaneously occurring tumor and its origin, develop a clonally derived cell line(s), and test experimental chemical induction of leukemia for toxicity test methods development, in addition to investigating its impact upon the interpretation of chronic toxicity results in the NTP.

FY 1984 ACCOMPLISHMENTS

A reproducible MNCL transplant model was established in male F344/N rats. This transplant model has been characterized in terms of its clinical presentation, gross pathology, cell morphology and biochemistry, histopathology, and clinical hematology and chemistry. After subcutaneous inoculation of 2×10^7 viable leukemic cells, clinical symptoms, morbidity and mortality due to MNCL occur after 100 days (95 to 105 days). Clinical symptoms are usually

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present after 90 days. However, with this size inoculum, splenomegaly and leukocyte count increases start to occur after 65 days. The transplant model has been determined to be morphologically and pathologically indistinguishable from spontaneous tumors. However, the pattern of biochemical response in spleen and blood mononuclear cells from transplant cases was inversely related to the enzyme elevations previously noted in spontaneously leukemic rats. (CONTACT PERSON: Dr. J. French)

FY 1985 PROGRAM PLANS

The objective is to design and develop a short-term (accelerated) chemical treatment test model in MNCL transplanted Fischer 344/N male rats for investigating the relationship between chemical treatment and the occurrence of MNCL in NTP chronic toxicity tests. (CONTACT PERSON: Dr. J. French)

Leukemia Research Program -- The effect of chemicals on the potentiation of leukemogenesis is being studied in a Fischer 344 rat leukemia model. The cellular biochemical responses in separated reticulo-endothelial cell populations from blood and spleen are being evaluated to support the NTP effort to characterize and define Fischer 344 rat leukemia. (CONTACT PERSON: Dr. M. Dieter)

Metal Toxicology

The effect of inorganic or organic metals and metal complexes is of particular interest to the NTP because of their prevalence in drinking water and industrial processes, use as constituents in anticancer drugs, and their diverse target organ toxicities.

Mechanisms of cellular toxicity to metals are being studied in collaboration with the immunotoxicity and leukemia research programs, and to support the carcinogenesis and toxicology research performed at contract laboratories.

FY 1984 ACCOMPLISHMENTS

Mercuric Chloride -- This chemical was studied in an extended prechronic test in rats and mice. Rodents were gavaged with graded doses of mercuric chloride, and urinary enzymes were evaluated at 12, 120, and 180 days to determine their utility as predictors/indicators of tubular nephrotoxicity. Of seven enzymes evaluated, the most sensitive responders were alkaline phosphatase and glutamic oxalacetic transaminase, and those responding with the greatest magnitude of change were lactate dehydrogenase and gammaglutamyl transpeptidase. Other indicators of renal toxicity, such as serum urea nitrogen and serum creatinine and serum enzymes, did not change. Histopathological evidence of toxicity was correlated with urinary enzyme responses at 12 days, but not at 120 and 180 days. (CONTACT PERSON: Dr. M. Dieter)

Titanocene Dichloride -- This chemical was studied in a 90-day prechronic test in rats and mice. Rodents were gavaged with graded doses of titanocene dichloride and the distribution and accumulation of titanocene in target organs was evaluated. There was dose-dependent accumulation of titanocene in the heart, liver, lung, and spleen. Concentrations of metal were highest in the spleen, followed in order by the liver, lung, and heart. There was no difference in target organ accumulation between species, but male rats and mice consistently accumulated higher concentrations of titanocene in target organs than did female rodents. (CONTACT PERSON: Dr. M. Dieter)

FY 1985 PROGRAM PLANS

Mercuric Chloride -- Urinary enzyme responses will be evaluated after 15 months exposure to graded gavage doses of mercuric chloride to further characterize the chronic effects of chemical treatment, and to determine the utility of urinary enzyme assays as predictors/indicators of chronic tubular nephrotoxicity. (CONTACT PERSON: Dr. M. Dieter)

Titanocene Dichloride -- Further accumulation of titanocene in target organs will be documented after 15 months exposure to the chemical and the hematological responses also evaluated.

After 18 months exposure to the metal, rats will be evaluated for the prevalence of F344 rat leukemia and the effect of titanocene dichloride on this disease, since earlier work indicated that the metal induced leukemia originating in the spleen. For this purpose, rats exposed at a contract laboratory will be transported to NIEHS for evaluation by procedures utilized in the leukemia research program. (CONTACT PERSON: Dr. M. Dieter)

Nickel Sulfate -- The chemical will be administered in the drinking water at graded doses to examine the toxicological effects of nickel sulfate on lymphocytes, granulocytes and macrophages separated from bone marrow, thymus, spleen, and lymph nodes, since there is evidence that nickel is an immunoeffective agent and alters cells of the reticulo-endothelial system. This study will be a collaborative effort with the immunotoxicity program to study the immune response, bone marrow stem cell responses, and metal accumulation and distribution. (CONTACT PERSON: Dr. M. Dieter)

Butadiene Initiative

1,3-Butadiene (butadiene) is a high production chemical (nearly 2 billion pounds per year in the United States) which is used as an intermediate in the production of elastomers, polymers, and other chemicals. Approximately 62,000 workers are exposed annually to butadiene, with the majority of exposures occurring at sites of manufacture of elastomers and polymers using butadiene (e.g., synthetic rubber producers). In a recent NTP chronic inhalation study in $B6C3F_1$ mice, butadiene was found to induce neoplastic lesions at multiple target sites at exposure levels below the threshold limit value (TLV) for this chemical.

FY 1985 PROGRAM PLANS

Additional inhalation toxicology studies have been designed to characterize the dose response for butadiene-induced neoplastic and non-neoplastic lesions in mice, and to characterize the toxicity of butadiene in rats. Pharmacokinetic studies of butadiene have been initiated to determine whether differences in species sensitivities to this chemical are due to differences in absorption, metabolism, excretion and/or other dispositional factors. Assessments of the immunosuppressive and teratogenic potentials of butadiene are also included in this initiative.

Finally, two structural analogs of butadiene, chloroprene (2-chloro-1,3-butadiene) and isoprene (2-methyl-1,3-butadiene), will be studied for their toxicologic potentials. Subchronic (14-day and 13-week exposures), chronic (2-year exposure), pharmacokinetic, and teratogenicity studies of chloroprene and isoprene have been planned. (CONTACT PERSON: Dr. R. Melnick)

Evaluation of Microencapsulation for Toxicology Studies

Microencapsulation, a process in which a thin and continuous polymeric coating is applied onto small particulate solids or liquid droplets, is being evaluated as a means of administering reactive, volatile, or unpalatable chemicals into rodent feed for toxicology studies.

FY 1984 ACCOMPLISHMENTS

Trichloroethylene and 2,6-xylidine, two volatile chemicals, have been separately encapsulated in gelatin-sorbitol microcapsules. These formulations provide sufficient stability to the chemicals so that they may be useful in dosed-feed toxicology studies. Studies have begun comparing the rates and extents of absorption of these chemicals, either neat or microencapsulated, in rats and mice. (CONTACT PERSONS: Dr. C. W. Jameson, Dr. R. Melnick, and Dr. T. Goehl)

FY 1985 PROGRAM PLANS

14-Day dosed-feed toxicity studies have been planned to evaluate the toxicologic potential of these chemicals when administered in microcapsules and to verify the stability of dosed-feed mixtures. (CONTACT PERSON: Dr. R. Melnick)

Superfund Project

(Interagency Agreement Between the Agency for Toxic Substances
and Disease Registry and the National Toxicology Program)

This Interagency Agreement was initiated on July 26, 1983. Under this agreement, the NTP will provide toxicological testing of chemicals to support health related activities of the DHHS, as conducted under the Comprehensive Environmental Response, Compensation and Liability Act of 1980 (CERCLA; Superfund Act). Twenty-four chemicals (including isomers) were nominated to the NTP for testing from the Environmental Protection Agency (EPA), the Hazardous Waste Information Evaluation Subcommittee (HWIES) of the DHHS Committee to Coordinate Environmental and Related Programs, or the NTP Chemical Selection Committee. The necessity, nature, and scope of testing are determined by NTP in accordance with the Program's established procedures.

FY 1984 ACCOMPLISHMENTS

A Chemical Manager (toxicologist) was hired by the NTP to handle Superfund-related testing. NTP Superfund activities at the end of FY 1984 are as follows:

1. Mutagenicity Testing: Testing of ethylbenzene is ongoing in Salmonella, and it is also being tested for cytogenetic effects.

2. Chronic Toxicity Testing: Toluene is undergoing chronic testing.

3. Fertility and Reproductive Testing: Five phthalates are being tested under the continuous breeding protocol.

4. Chemical Disposition/Structural Activity: Five chemicals (mono- and dichlorobenzenes, 1,2,4,5-tetrachlorobenzene, chloroform and trichloroethylene) are undergoing testing. (CONTACT PERSON: Dr. R. Yang, NIEHS)

FY 1985 PROGRAM PLANS

An additional Chemical Manager is to be hired to handle the Superfund testing activities. Other chemical managers on the NTP staff will assist on the Superfund Project as needed. Three areas to be pursued are:

1. Filling of data gaps on single chemicals - this involves the evaluation of the existing information, the identification of data gaps and the recommendation of appropriate testing to fill in the data gaps. It is anticipated that 15-20 chemicals will be reviewed internally in FY 1985.

2. Formulating plans to test toxicological interactions between (among) two (or more) chemicals.

3. Exploring ways to evaluate the toxicity of chemical mixtures of higher order (i.e., more than 2 or 3 chemicals) or the toxicity of samples from priority hazardous waste sites. (CONTACT PERSON: Dr. R. Yang)

Biochemical Toxicology

The liver metabolizes foreign compounds to both inactive and reactive (mutagenic or toxic) metabolites. Exposure to foreign chemicals alters the terminal monooxygenases responsible for metabolism of many of these compounds. Moreover, changes in monooxygenases and epoxide hydrase are among the early changes which occur in neoplastic nodules suggesting that they are part of a gene battery which is affected early in the neoplastic process.

The NIEHS/NTP biochemical toxicology program is involved in characterization of changes in the monooxygenase system which occur after exposure to environmental chemicals. Present work involves purification of isozymes, and development of antibodies and immunological procedures and other sensitive methods for identifying and quantitating changes in isozymes in rats. This work also involves assessment of the contribution of these cytochromes to the formation of toxic and mutagenic products.

FY 1984 ACCOMPLISHMENTS AND FY 1985 PROGRAM PLANS

1) The two 3-methylcholanthrene (MC) inducible isozymes (P-448-MC and P-448-HCB) were active in the metabolism of 2-acetylaminofluorene in the rat. P-448-MC was most active in ring hydroxylation

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(detoxification) while P-448-HCB was more active in toxification (N-hydroxylation).

2) The induction of P-448-MC and P-448-HCB has been studied after administration of different doses of a polychlorinated biphenyl (PCB) isomer. The two isozymes are induced coordinately in the liver and a qualitatively similar effect on translation was noted. However, in extrahepatic tissues the induction of the two proteins was disassociated.

3) Preliminary work on an isozyme induced by clofibrate indicates that it is also induced by affecting translation. This isozyme appears also to be induced by phthalates. Additional isozymes are being isolated and antibodies raised. Methodology is being tested to provide the easiest and most reliable methods for identifying changes occurring after administration of environmental chemicals as well as between sexes and during aging. Attempts will be made to clone cDNA complementary to mRNA for the rat P450s for this purpose. Studies on lauric acid and prostaglandin metabolism have also been initiated. (CONTACT PERSON: Dr. J. Goldstein)

NIOSH

FY 1984 ACCOMPLISHMENTS

Cardiac Toxicology -- During FY 1984, groups of Fischer 344 rats were injected with isoproterenol and norepinephrine in order to induce cardiac fibrosis and hypertrophy, respectively. Animals were evaluated for up to three weeks using electrocardiography and pathology to assess the development of fibrosis and hypertrophy. Compound-specific electrocardiographic alterations were found in the rats administered these agents. Limb and chest leads, as used in human electrocardiography, proved to be more sensitive in detecting cardiac changes than the standard approach previously used in rodents. The pathological evaluation of tissues from rats previously exposed to ethylamine and allylamine continued this year. Work with carbon disulfide (CS_2) was involved with the set-up and analytical verification of targeted CS_2 exposure concentrations. (CONTACT PERSON: Mr. D. Lynch)

FY 1985 PROGRAM PLANS

Cardiac Toxicology -- Six-month exposures of rats to CS_2 will be completed and data analyses will begin. The objective of these studies is to evaluate the impact of CS_2 induced thyroid gland toxicity on the subsequent development of atherosclerotic disease. The overall goal of this work is to develop and validate methods which will predict cardiotoxic events in animals exposed to occupational toxicants.

General Toxicology -- Six-month exposures of rats will be made to compare the toxicities of lead sulfide and lead oxide and of vanadium pentoxide and vanadium trioxide for evaluation of common exposure standards, based on the metals, for miners. In another study, the effects of supplementary zinc and copper in the diet on the pathology of rats exposed to a mixture of carbon disulfide and hydrogen sulfide will be evaluated. (CONTACT PERSON: Dr. T. Lewis)

THE BENZIDINE-DYE INITIATIVE

The benzidine-dye initiative was designed to study the toxicology and carcinogenicity of a class of dyes derived from either benzidine, 3,3'-dimethylbenzidine, or 3,3'-dimethoxybenzidine. This group of dyes includes some 82 discrete chemicals which are available in the United States. Human exposure results from contact with finished products (paper, fabrics, leather) to which the dyes have been applied, packaged dyes for home use, and the use of arts and crafts products such as spray paints, enamels, and lacquers. It has been estimated that approximately 1,000 workers are exposed to these materials during dye manufacturing and that perhaps as many as 15,000 workers are exposed in the various dye application industries.

Because of the high cost and time requirements for long-term studies in rats and mice, no attempt was made to routinely test all benzidine and benzidine congener dyes in the NTP program. Instead, an interdisciplinary chemical class toxicology program was designed and testing began in FY 1981. The objective of this program has been to develop an integrated body of scientific knowledge concerning the pharmacokinetics, genetic toxicology, and *in vivo* toxicity and carcinogenicity of the benzidine congeners as a class and for selected prototypical dyes. Through the careful selection of chemicals for testing, it should be possible to establish basic principles which can be applied to the entire class of benzidine-based dyes.

The program was developed in response to the needs of EPA, CPSC, and OSHA. The scientific objectives and approaches were formulated by scientists from the EPA, CPSC, OSHA, NCI, NIEHS, NCTR and NIOSH. As designed, the program is providing the scientific information required for making regulatory decisions about benzidine and benzidine congener-based dyes and serving as a model for future chemical class studies. (CONTACT PERSON: Dr. J. H. Mennear)

NIEHS

FY 1984 ACCOMPLISHMENTS

Chemical Disposition Studies -- All planned pharmacokinetic studies (see Table 15) have been completed. Through the use of orally administered parent amines and representative dyes, the absorption, distribution, metabolism and excretion of these chemicals were studied in rats. While projected plans for C.I. Direct Blue 218 (FY 1983 *Annual Plan*) included the synthesis of ^{14}C-labeled dye and the conduct of pharmacokinetic studies, technical difficulties precluded the preparation of a sufficiently pure sample of the labeled dye. Both radiochemical and chemical impurities were such that they would have severely compromised the validity of a pharmacokinetic study. This phase of the program is now completed. (CONTACT PERSONS: Dr. C. W. Jameson and Dr. H. B. Matthews)

Genetic Toxicology -- The mutagenicity testing of urine samples collected during the metabolism studies reported above has been completed. Urine samples were chemically analyzed for suspected mutagenic metabolites of dyes, then tested in *in vitro* protocols. All samples produced negative results, a finding consistent with the low concentrations of metabolites detected chemically. (CONTACT PERSON: Dr. E. Zeiger)

In Vivo Toxicology and Carcinogenicity Testing -- Two-year studies on dimethylbenzidine, dimethoxybenzidine, C.I. Direct Blue 15 and C.I. Acid Red 114 in rats were initiated and 40-week interim kills were conducted.

The 13-week studies on C.I. Direct Blue 218 in rats and mice were completed during FY 1984. Based upon the results of these studies a decision has been made to pursue chronic testing with this chemical. (CONTACT PERSON: Dr. J. H. Mennear)

FY 1985 PROGRAM PLANS

Chemical Disposition Studies -- All planned studies have been completed. No further work is anticipated.

Genetic Toxicology -- All planned studies have been completed. No further work is anticipated.

In Vivo Toxicology and Carcinogenicity Testing -- The in-life portions of the two-year studies on dimethylbenzidine, dimethoxybenzidine, C.I. Direct Blue 15 and C.I. Acid Red 114 will be completed. Final technical reports are planned for FY 1986.

The two-year study on C.I. Direct Blue 218 in rats and mice will be initiated during FY 1985. (CONTACT PERSON: Dr. J. H. Mennear)

TABLE 15

SUMMARY OF THE NTP BENZIDINE CONGENER INITIATIVE

Chemical	CAS No.	Tests[1]
Benzidine derived		
Benzidine	92-87-5	G,P,T[2]
C.I. Direct Blue 6	2602-46-2	G,P,T[2]
o-Dianisidine derived (3,3'-dimethoxybenzidine)		
o-dianisidine	119-90-4	G,P,T[3]
C.I. Direct Black 114	61703-05-7	G,M
C.I. Direct Blue 8	2429-71-2	G,M
C.I. Direct Blue 10	4198-19-0	G
C.I. Direct Blue 15	2429-74-5	G,P,T[3]
C.I. Direct Blue 218	28407-37-6	G,P,T[4]
C.I. Direct Violet 32	6428-94-0	G,M
o-Tolidine derived (3,3'-dimethylbenzidine)		
o-tolidine	119-93-7	G,P,T[3]
C.I. Acid Red 114	6459-94-5	G,P,T[3]
C.I. Direct Blue 25	2150-54-1	G
C.I. Direct Blue 53	314-13-6	G,M
C.I. Direct Orange 6	6637-88-3	G,M
C.I. Direct Red 2	992-59-6	G,M
C.I. Direct Red 39	6358-29-8	G,M

TABLE 15 (Continued)

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[1] Key: G = Genetic toxicology testing
P = Pharmacokinetic studies
M = Metabolism studies for detection of carcinogens in urine
T = Toxicologic and carcinogenesis bioassay

[2] Benzidine and Direct Blue 6 were comparatively studied in a 13-week feeding study in rats only.

[3] o-Tolidine, Acid Red 114, o-Dianisidine and Direct Blue 15 are being comparatively evaluated in two-year toxicology and carcinogenesis studies in rats only.

[4] Direct Blue 218 was tested in rats and mice in a 13-week study. Data from this study and genetic toxicology studies were used to determine that two-year toxicology and carcinogenesis studies are indicated.

CHEMICAL DISPOSITION

The immediate objective of chemical disposition studies is to provide information on the absorption, distribution, metabolism and excretion of chemicals or chemical classes chosen for testing by the NTP. This information is intended for use in the design, choice of dose and interpretation of results from studies of the toxicity and carcinogenicity of these chemicals. Long-range, but equally important, objectives of chemical disposition studies are to develop and publish data that will permit a better assessment of structure-activity relationships, which influence chemical disposition or mechanisms of toxicity and provide basic information for facilitating the extrapolation of laboratory data to man. Another objective is development of analytical methodology and data on metabolism, and use of this information in evaluating disposition in workers exposed to chemicals.

NIEHS

Major projects in the Chemical Disposition Section include studies of the metabolism and disposition of a variety of chemicals, investigations of mechanisms of toxicity and metabolism, and studies of the effects of age, body composition and route of administration on chemical disposition. Studies of metabolism and disposition have been designed and conducted for chemicals with a wide variety of properties and substitutions. Studies of the mechanisms of toxicity have addressed a variety of compounds ranging from the extremely toxic 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) to the much less toxic acrylates and include studies of environmental contaminants administered in binary combinations. Studies of the effects of age, body composition and route of administration on chemical disposition indicate that each of these factors can have very selective effects and that the importance of these effects vary with the chemical administered and the mechanisms involved in the metabolism and clearance of the respective chemical.

FY 1984 ACCOMPLISHMENTS

(1) a. Studies of the metabolism and disposition of benzyl acetate indicate that this compound is readily absorbed from the gastrointestinal tract, rapidly metabolized and rapidly excreted primarily in urine. Gastrointestinal absorption of benzyl acetate is not affected by dose in the range studied, 5 to 500 mg/kg in rats, 10 to 1000 mg/kg in mice. The major metabolite of benzyl acetate is hippuric acid which is excreted almost exclusively in urine. Metabolism is also unaffected by dose in the range studied. Studies of the dermal absorption of benzyl acetate demonstrate that this compound is absorbed through the skin but most of the dose is lost by evaporation. Therefore, the effective dose of benzyl acetate which can be administered dermally is limited by evaporation and the amount which can be applied without loss by runoff. Metabolism and distribution of a dermal dose of benzyl acetate are qualitatively similar to that observed for an oral dose.

b. Urinary metabolites of benzyl acetate in rat and mouse from a variety of treatment regimens were separated by HPLC using a C-18 column with a pH 6 phosphate buffer-acetonitrile solvent gradient. Hippuric acid, the major metabolite (>84% of total urinary metabolites in all samples), was identified by coelution with an authentic sample in two different solvent systems. S-Benzyl-N-acetyl-L-cysteine (benzyl mercapturic acid) was identified as the other major metabolite by coelution with a sample prepared from benzyl chloride and N-acetyl-L-cysteine using sodium bicarbonate as a catalyst. Small amounts (usually less than 1% of the total urinary metabolites) of benzyl alcohol were identified by coelution in some samples.

(2) Parameters governing studies of dermal absorption were investigated and showed that the effective dose of a chemical, i.e., that dose which is absorbed, which can be applied to the skin of a laboratory animal is limited by several factors. A large portion of a volatile compound applied to skin is lost by evaporation. The solvent in which a chemical is applied must be sufficiently volatile to prevent runoff or loss to contact with the cage, bedding, etc. The skin surface to which a chemical is applied must be sufficiently small to minimize the animal's licking the chemical from the skin and receiving an oral dose. It has been determined that there is no area on the back of a rat or mouse which the animal cannot scratch and thus remove a portion of the dose resulting in possible ingestion by licking of the feet. Repeated application of nonvolatile chemicals which are not readily absorbed may result in residues on the skin which may be lost by flaking off into the bedding. Direct loss from the skin by volatilization, runoff or sluffing of chemical residues is a major limitation on the effective dose which can be applied in studies of dermal toxicity. If the dose applied in dermal studies cannot be accurately quantitated, dose response curves are less meaningful.

(3) The gastric toxicity of a series of acrylate esters was studied, indicating that these compounds produce an immediate effect of severe edema in the forestomach of rats when administered by gavage. A less profound effect was observed on glandular stomach where toxicity was both dose and concentration dependent and varied with the vehicle and acrylate ester administered. Gastric toxicity was due to the acrylate ester administered and not to the hydrolysis products of the esters. Adaptation of rats to the toxic effects of nonlethal doses of acrylate esters is more manifest in the glandular stomach than in the forestomach where chronic doses of these compounds result in chronic irritation accompanied by the pathology expected of chronic irritation.

(4) The organic peroxide, t-butyl perbenzoate, was studied to determine stability in dosing medium and metabolic fate following administration to laboratory animals. The chemical was stable in corn oil and in albumin-buffered saline, and unstable in rat blood and stomach contents or when applied to rat skin. t-Butyl perbenzoate decomposed very rapidly in the presence of microsomal, soluble or plasma enzyme preparations. It could not be determined if this degradation was spontaneous or enzymatic. Following administration of ^{14}C-labeled t-butyl perbenzoate to adult male Fischer 344 rats by intravenous (i.v.) injection, the ^{14}C was rapidly excreted primarily in urine. Following dermal application approximately 15% of the dose was absorbed. t-Butyl perbenzoate did not persist in tissues following either route of administration.

(5) The effect of dose on the disposition of hexachloro-1,3-butadiene was studied demonstrating that this compound is absorbed from the gastrointestinal tract and eliminated in urine, feces and exhaled air. The major route of elimination is in feces while the portion excreted in urine is about one-third that observed in feces with only two to three percent being eliminated in exhaled air. The rate of hexachloro-1,3-butadiene elimination is affected by dose. As the dose is increased the rate of elimination in urine and feces decreases. Work still under way is designed to determine if this effect of dose is due to a decreased rate of absorption, altered metabolism or increased tissue accumulation.

(6) The fate of the swimming pool disinfectant, 1,3-dichloro-5,5-dimethylhydantoin (Cl-2-DMH), was studied in the rat. This compound was shown to rapidly lose a chlorine atom in an aqueous environment to form 1-chloro-5,5-dimethylhydantoin (Cl-1-DMH). Cl-1-DMH is relatively stable in aqueous solution over a pH range from 1.7 to 7.0 but is rapidly degraded in blood. In in vitro experiments less than 0.2% of Cl-1-DMH remained intact following a one minute incubation in whole blood at 37°C. Dimethylhydantoin (DMH) accounted for greater than 85% of the reaction product of Cl-1-DMH in blood. When Cl-2-DMH and DMH were administered to intact animals in separate experiments, greater than 80% of the dose was excreted in urine in 24 hours with DMH accounting for greater than 90% of the material excreted in urine following administration of either Cl-2-DMH or DMH. Neither compound concentrated in tissues and within 72 hours after dosing less than 1% of the dose of either compound was retained by the animal.

(7) The fate of crotonaldehyde-^{14}C was studied under both in vivo and in vitro conditions to determine stability under biological conditions and to provide information on the metabolism and disposition of this chemical in higher animals. In vitro, crotonaldehyde is stable in rat blood plasma over 30 minutes. In vivo, greater than 90% of an oral dose of crotonaldehyde is absorbed from the gastrointestinal tract and absorption is not altered by dose in the range of 0.7 to 35 mg/kg. Following absorption, crotonaldehyde is rapidly metabolized and excreted. Following an iv dose, 33% was eliminated as CO_2, and 40% in urine in six hours. Parent compound accounted for less than 1% of the material excreted in urine and crotonic acid accounted for less than 2% with most of the dose eliminated as an unknown metabolite. Less than 1% of the dose was eliminated in feces. There was no evidence that crotonaldehyde or its metabolites accumulated in tissues.

(8) The disposition of ^{14}C-labeled 2-mercaptobenzimidazole was studied in young adult male rats. This compound was readily absorbed from the gastrointestinal tract and rapidly metabolized. 2-Mercaptobenzimidazole was rapidly distributed to all tissues following i.v. administration, but did not concentrate in any tissue. Most of the radioactivity in tissues was in the form of metabolites, but significant amounts of the parent compound were found in most tissues at the early time points. However, only traces of the parent compound were excreted. The major route of 2-mercaptobenzimidazole excretion was urine (approximately two-thirds of the dose). The major metabolite excreted was identified as benzimidazole. Neither the rate nor the routes of 2-mercaptobenzimidazole absorption, metabolism and clearance were greatly affected by dose over a range of 0.5 to 49 mg/kg.

(9) 9-Aminoacridine hydrochloride has broad spectrum antimicrobial properties and is used as a topical antiseptic. The fate of ^{14}C-labeled 9-aminoacridine was investigated in laboratory animals to determine absorption following oral and dermal exposure and the potential of this chemical to accumulate in the tissues of higher animals. This chemical is very poorly absorbed from the skin by both rats and monkeys. On the other hand, 9-aminoacridine hydrochloride was readily absorbed from the gastrointestinal tract of rats. Following oral or i.v. dosing this compound was excreted primarily in feces and secondarily in urine. Excretion of an oral dose was near complete in 24 hours; thus, this compound does not appear to concentrate in the tissues of higher animals.

(10) Decabromodiphenyl oxide is a completely halogenated aromatic chemical commonly used as a fire retardant and the subject of a recently completed study of chronic toxicity and carcinogenicity. Due to insolubility, poor and highly dose dependent absorption was expected from the gastrointestinal tract. Therefore, a study of the gastrointestinal absorption of decabromodiphenyl oxide was initiated at a series of doses ranging from 0.025 to 5.0% in the diet.

(11) Interactive toxicity studies of a series of eight chemicals in *in vivo* and *in vitro* systems were initiated. Those combinations of chemicals showing greater than additive toxicity in preliminary studies will be studied further to determine if observed toxicity is due to altered metabolism and disposition. Studies to date include the following:

a. An *in vivo* interaction study with nontoxic doses of two halogenated hydrocarbons, carbon tetrachloride and trichloroethylene, resulted in elevated serum glutamic pyruvic transaminase (SGPT) activities in F344 rats. This interactive toxicity, which is dose dependent for both trichloroethylene and carbon tetrachloride, has been reproduced using trichloroethylene administered in drinking water and a toxic challenge by an intraperitoneal (i.p.) dose of carbon tetrachloride. Under these conditions SGPT levels were increased in a synergistic fashion when compared with levels in animals treated with either chemical alone, and as observed previously, the effect was dose dependent for both compounds.

b. Chronic exposure (23 weeks) of rats to trichloroethylene or carbon tetrachloride and assessment of hepatotoxicity by a battery of assays indicate that chronic exposure to these compounds at relatively low doses will result in hepatotoxicity. Therefore, animals exposed to these and similar compounds may be predisposed to toxic insult by other chemicals and/or chemical combinations.

c. Assays using isolated hepatocytes are being developed to predict hepatotoxicity mediated by halogenated hydrocarbons and assess hepatotoxicity from interactive combinations of chemicals. Results indicate hepatocytes isolated from animals previously treated with a known inducer of hepatic mixed-function oxidases, phenobarbital, are more sensitive to the toxic effects of chlorinated benzenes than are hepatocytes isolated from control animals. This system will be developed further and used to assess the potential hepatotoxicity of additional halogenated chemicals and combinations of halogenated chemicals.

(12) The disposition of halogenated dibenzofurans and dibenzodioxins was studied in different species and animal strains with the following results:

a. Upon repeated exposure of guinea pigs to low levels of 2,3,7,8-tetrachlorodibenzofuran (TCDF), intoxication does not occur until a critical body burden, primarily in the fat, is reached. At this point extensive weight loss and death ensue rapidly. The repeat dose studies indicate that the fat content affects the amount of TCDF needed to reach toxicity. Mature animals have larger fat deposits and have a higher LD_{50} than observed for young animals. The time to death also seems to increase with age while a lower percentage of the body weight seems to be lost before death occurs.

b. Studies with DBA non-responsive (Ah receptor negative) and C57BL responsive (Ah receptor positive) mice with TCDF suggested that body composition could modulate the toxic response observed in these mice, i.e., "fat" mice (DBA) were less sensitive to the toxic actions of compounds like TCDD than were "lean" mice (C57BL). The strains differ at the Ah locus, which may mediate the toxic response to TCDD and congeners. However, these strains differ at many other loci. To test the role of body composition vs. the Ah locus, congenic mice were obtained from Dr. A. Poland (University of Wisconsin). The distribution and excretion of ^{3}H-TCDD were examined in two groups of mice, DBAs, both responsive and non-responsive, and C57BLs, both responsive and non-responsive. The elimination kinetics were independent of the Ah locus, varying instead with body composition as predicted.

(13) Senescent changes in laboratory rats which affect chemical metabolism, disposition and/or toxicity were studied indicating the following:

a. Altered pharmacological responses - Previous investigations analyzed age-related changes in hepatic drug metabolism *in vitro*, specifically alterations in the mixed-function oxidase system. Currently, work is in progress to explore aging effects on glucuronyl transferase and β-glucuronidase activity in liver, lung, kidney, and small intestine. No changes in specific activity of either enzyme were observed in extracts from lung or intestine among animals of 3,6,12,18, and 32 months of age. In both liver and kidney there was a decline in activity of glucuronyl transferase with p-nitrophenol as a substrate between 2 and 6 months of age, while glucuronidation with phenolphthalein as a substrate increased after 78 weeks of age. β-Glucuronidase activity increased in kidney homogenates and microsomes as the rats aged. The enzymatic changes are being evaluated for correlations with pathological alterations as well. For instance, approximately 20% of the older rats have Fischer rat leukemia. The above enzyme activities are different in leukemic animals from those in the healthy age-matched controls.

b. Changes in the disposition of two polychlorinated biphenyls (PCBs) in aging rats have been examined. 2,3,6,2',3',6'-hexachlorobiphenyl(236) and 2,4,5,2',4',5'-hexachlorobiphenyl(245) are symmetrical isomers whose distribution, metabolism, and excretion in young rats have been previously studied in our laboratory. Senescent rats (22-24 months) were given ^{14}C-labeled 236 or 245 (0.6 mg/kg) i.v. from one hour to 21 days and distribution was examined in tissues and excreta. Half-lives and pool sizes were increased for both compounds, suggesting a slower rate of metabolism. Increased metabolite/parent ratios in the tissues suggested a slower elimination of metabolites in the old rats. Since the effects of aging seem to be more pronounced for 245 than for 236, senescence may differentially affect the disposition of more persistent PCBs. Age-related changes in body composition seem to modulate the dispositional properties.

c. Age-related changes in absorption of xenobiotics from the small intestine are being investigated using the technique of *in situ* luminal perfusion. Initially, both passive and active transport will be compared in young (2 month) and old (27 month) rats using model compounds. Preliminary studies have shown no decrease in passive absorption of 2-deoxy-d-glucose in 24-27 month old male rats as compared to that observed in 2 month old rats. Active transport of 3-O-methylglucose was half as rapid in old rats. Chemicals of environmental interest will be evaluated to see if age-related effects on absorption occur.

d. Alterations in intermediary metabolism in lymphoid tissue - Lymphatic tissues and associated cells, including thymus, spleen, and macrophages, were examined for age-related changes in intermediary metabolism. Key enzymes from the hexose monophosphate shunt, glycolysis, and the Krebs cycle were compared in rats of 6,12,18, and 24 months of age. Pyruvate kinase and lactate dehydrogenase decreased in thymus, but increased in spleen. Glucose-6-phosphate dehydrogenase, isocitrate dehydrogenase, and malate dehydrogenase activities all decreased in pulmonary macrophages. These data suggest that the biochemical support for phagocytosis and cell mediated immunity are diminished during aging in macrophages and in the thymus, while the humoral immune response mediated by splenic B cells may not be compromised in senescent rats.

(14) The disposition of Santonox (4,4'-thio-bis(6-tert-butyl-m-cresol) was studied revealing that absorption was incomplete after oral exposure. The rate of absorption was decreased with increasing dose due to enhanced retention in the stomach, which also resulted in severe irritation and ulceration. This irritant effect was not due to the vehicle or the volume used, but was a reflection of the actual amount of Santonox delivered by a bolus gavage dose. On reaching the small intestine, absorption was proportional to the dose. Treatment by the i.v. route resulted in rapid distribution from the the blood to the rest of the body with the principal depots at early times being liver, muscle, skin and adipose tissue. Santonox was rapidly metabolized by the liver and excreted primarily via the bile into the feces. Some of the parent compound tended to persist in the liver, skin, and adipose tissue suggesting accumulation might occur upon chronic exposure. Glucuronide conjugates appear to be the major metabolites of Santonox. Techniques used involved liquid chromatography (HPLC)-mass spectroscopy. The O-glucuronide was confirmed as the major (>=90%) metabolite.

(15) Bromonapthalenes have no known industrial use or application, but have been identified as contaminants of Firemaster BP-6, the mixture of polybrominated biphenyls used as a fire retardant and involved in a major episode of environmental poisoning in Michigan. Structurally related to other halogenated aromatic xenobiotics, their toxicity and disposition seem to vary with the position of bromination. This work has studied the chemical disposition of a mixture of two-hexabromonapthalenes (HBNs), previously identified as a single isomer, 1,2,3,4,6,7-HBN. The compound is incompletely absorbed after an oral dose. After i.v. treatment over 50% of the dose is excreted as metabolites within 3 days with over 25% remaining in the liver after 35 days. These results led to confirmation of two isomers by high resolution NMR, present in a ratio of 60:40, and tentatively identified as 1,2,3,4,6,7 and 2,3,4,5,6,7-HBN. Studies of the fate of the two isomers showed that while the HBN dose was in the isomeric ratio of 60:40 (1,2,3,4,6,7: 2,3,4,5,6,7), the HBN in the liver 10 days after oral treatment was in the ratio of 20:80. The toxicity of this HBN mixture is also being studied, and will include an analysis of the teratogenicity of HBN, both alone and in combination with polybrominated biphenyls.

(16) Benzo(f)quinoline (BQ) disposition was examined in the rat indicating that BQ was completely absorbed from the gut and concentrated in the liver. Much of the compound was rapidly metabolized in the liver and excreted in approximately equal amounts via the bile into feces or via the kidneys into the urine. A portion of the total dose is distributed to the fat and skin, then recirculates to the liver. By 72 hours, less than 2% of the dose is retained in the body. The majority of the tissue radioactivity is due to unmetabolized BQ, while most of that excreted represents oxidation products of the parent compound. The metabolites of BQ will be further characterized and the possibility of covalent binding to tissue macromolecules investigated.

(17) O-Benzyl-p-chlorophenol (BCP) is a broad spectrum germicide which is highly irritating and causes renal necrosis. Oral treatment for 3 days with BCP resulted in an increase in the amount of cytochrome P450 present in both hepatic and renal microsomes. The cytochrome P450 species were partially resolved by HPLC and a specific peak was shown to respond to BCP treatment. This peak does not co-chromatograph with the cytochromes induced by 3-methylcholanthrene (3-MC), clofibrate or PCN but does migrate with the form induced by phenobarbital. Further work to identify this species is in progress. BCP treatment also seems to inhibit arylhydrocarbon hydroxylase activity. The mechanism of this inhibition is being investigated.

(18) 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) was studied for teratogenicity in combination with other chemicals providing strong evidence for interactive toxicity with this potent teratogen. Studies of two PCBs having a similar degree of chlorination, but different stereochemical configurations indicate that sterochemical considerations may be critical to toxicity. The non-planar symmetrical isomer 2,4,5,2',4',5'-hexachlorobiphenyl (HCB) had no effect on TCDD teratogenicity. However, 2,3,4,5,3',4'-HCB administration enhanced the frequency of cleft palate in a dose-related manner. Similarly, thyroid hormones T_3 and T_4 (thyroxine) enhance the induction of cleft palate by TCDD in a dose related fashion with a dose of 250 µg/kg T_3 resulting in a 5-fold increase in teratogenicity. T_3 is about five-fold as potent as T_4.

(19) The disposition of 2,3-dichloropropene (DCP), a chemical present with other chloropropene isomers in commercially used soil fumigants, was studied. Recovery of radioactivity derived from ^{14}C-DCP was compared after oral and i.p. exposure of rats. The radioactivity was excreted via the urine (66-76%), feces (13-21%), and as CO_2 (8%) with only 2% exhaled as unchanged DCP. After 72 hours, only 2-3% of the dose remained in the carcass. More than 90% of an oral dose was absorbed. After inhalation exposure, absorption (35%), metabolism and excretion were linear over a 100-fold dose range, from 1.3 to 180µg ^{14}C-DCP vapor per liter of air for 6 hours. Approximately 50% of the ^{14}C was recovered in urine, 15% in feces, and 8% was CO_2 with most of the remainder adhering to the pelt. There was no evidence of tissue accumulation and essentially all the ^{14}C excreted was as metabolites of DCP. Tissue distribution, clearance, and time to steady state also have been determined.

(20) The disposition of methyl bromide (MB) was studied following various routes of exposure. Recoveries of oral and i.p. doses indicated little radioactivity persisted in the body after 3 days with urine being the major route of excretion. No changes in respiratory pattern occurred. Pulmonary absorption after inhalation exposure was linear over a dose range from 50 to

10,400 nmoles ^{14}C-methyl bromide/liter of air for 6 hours, decreasing only at higher doses. Expired CO_2 was the dominant excretory product. After 60 hours 25% of the dose remained in the body of rats. Time to steady state, tissue distribution and clearance profiles are being determined.

(21) Methods are being developed for the administration of azodicarbonamide (ADA) as a dust. Using a fluidized bed generator after milling, an aerosol with a concentration of approximately 160 mg ADA/m^3 and a mass median aerodynamic diameter (MMAD) of 3.9 µm was produced. This should result in an approximate pulmonary deposition of 1.2 mg ADA/rat using a 6 hour exposure. However, use of a Wright dust feeder has enabled generation of even smaller particles having a MMAD of < 3 µ over a dust generation range from 2 to 200 mg ADA/m^3. Three doses within this range are being used to determine the effect of dose on pulmonary absorption and on excretion after inhalation exposure. Excretion after intratracheal and oral administration were compared, with more being excreted in urine after intratracheal administration. Absorption was decreased after oral exposure. Time to steady state, tissue distribution and clearance will be examined.

(22) 1,2-Dihydro-2,2,2-trimethylquinoline (TMQ) was readily absorbed from the gastrointestinal tract of male rats, distributed to all tissues examined, and rapidly excreted primarily in the urine and to a lesser extent in feces. TMQ was excreted in the form of several metabolites and did not accumulate in any particular tissue. Clearance from the tissues was rapid so that 72 hours after administration less than 5% of the dose was present in the body. Radioactivity extracted from major tissues was primarily in the form of metabolites except in skin and muscle which contained only parent compound. In vitro, TMQ is readily metabolized by hepatic mixed-function oxidases. Some of the initial metabolites may be conjugated prior to excretion.

(23) The fate of methyl carbamate (MC) was studied in rats and mice. MC was readily absorbed from the gastrointestinal tract and rapidly distributed to all tissues examined in both species. The tissues of both species retained approximately the same amounts of MC-derived radioactivity at the early time points (15 minutes to 2 hours). Within 72 hours, less than 5% of the dose remained in mouse tissues. Approximately 80% of a dose was eliminated by mice in the expired air, 14% in urine and 4% in feces. On the other hand, clearance of MC-derived radioactivity from rat tissues was much slower and over 50% of the dose was still present in the tissues 72 hours after administration. By this time, 23% of the dose had been eliminated in the expired air, 19% in urine and 3% in feces. Multiple exposures of rats and mice to MC resulted in some bioaccumulation in all rat tissues examined but not in mouse tissues. No covalent binding of MC and/or metabolites to rat or mouse liver or muscle DNA was detected. A single metabolite was detected in rat and mouse urine. In vitro studies have also shown that MC is metabolized to some extent by rat and mouse liver subcellular fractions.

(24) The major urinary metabolite of allyl isothiocyanate in the rat was isolated and purified using a reversed phase preparative HPLC column with water-acetonitrile as the eluent. The NMR spectrum of the isolated compound was obtained at 360 MHz in deuterated methanol. The compound was identified as N-acetyl-S-(N-allylthiocarbamoyl)-L-cysteine, a mercapturic acid conjugate. This conjugate was chemically synthesized from allyl isothiocyanate and

N-acetylcysteine using potassium carbonate as a catalyst. The HPLC retention time and the NMR spectrum of the synthetic product was identical to the isolated metabolite.

(25) Major urinary metabolites of 2,4-dinitroaniline in rat urine samples were separated by HPLC using a C-18 column with a dilute acetic acid-acetonitrile solvent gradient. The separation conditions were then used in an HPLC-MS system and mass spectra of the major metabolites were obtained. The mass spectra were consistent with the major metabolite being N-(2,4-dinitrophenyl)hydroxylamine-O-sulfonic acid. N-(2,4-Dinitrophenyl) hydroxylamine was also present in lesser amounts.

(26) Chemical mechanisms for cytochrome P-450 metabolism have been investigated using correlation of Vmax and Km to Hammett's sigma parameter and Hansch's hydrophobic pi parameter. It has been found that the difference in regiospecificity in hydroxylation of monohalobenzenes by phenobarbital and beta naphthoflavone induced microsomes is due to a difference in chemical mechanism. The electronic demand for the rate determining step for N- and O-dealkylations has been investigated using the same correlations and evidence has been obtained that supports rate limiting one electron oxidation of the amine nitrogen to the radical cation. A corresponding one election oxidation of the ether oxygen apparently does not occur. (CONTACT PERSON: Dr. H. B. Matthews)

FY 1985 PROGRAM PLANS

A number of ongoing studies of chemical disposition in laboratory animals will be completed in FY 1985. New studies of chemical metabolism and disposition will be initiated as requested by the NTP or intramural personnel. Studies of mechanisms of chemical metabolism and toxicity will be continued. These studies will include in vivo and in vitro assays for interactive toxicity, investigations of species, sex and dose related toxicity and investigations of chemical and biochemical parameters which determine absorption, distribution and excretion of chemicals. (CONTACT PERSON: Dr. H. B. Matthews)

NIOSH

FY 1984 ACCOMPLISHMENTS

2-Ethoxyethanol -- Metabolism and excretion studies were completed in male Sprague-Dawley rats. Urine is the major route of excretion after oral administration, accounting for 76-80% of the dose by 96 hours. Major urinary metabolites recovered were ethoxyacetic acid and its glycine conjugate, N-ethoxyacetyl glycine. The biological half-time for the compound was between 10 and 13 hours. Results are in press in Environmental Health Perspectives. (CONTACT PERSON: Mr. K. Cheever)

Biological Monitoring -- Analytical procedures were developed for cadmium, mercury, and methylene dianiline in urine and for urinary metabolites of hexane, methyl butyl ketone, xylene and 2-ethoxyethanol. Procedures were also developed for 2-methoxyethanol, 2-ethoxyethanol, 2-butoxyethanol, methyl ethyl ketone (MEK) and toluene in blood. Quantitative high pressure liquid chromatography (HPLC) procedures were developed for mandelic acid and phenylglyoxylic acids in urine from rats dosed with $[C^{14}]$ labeled ethyl benzene. Urine samples were analyzed for these acids by these methods and by isotachophoresis for comparison. The data are being analyzed. An interlaboratory study of a previously developed analytical method for 4,4'-methylenebis(orthochloroaniline) (MBOCA) was undertaken, using urine samples from exposed workers. Evaluation of workers exposed to 2-ethoxyethanol is under way, using the methods developed for the chemical in blood and its metabolite in the urine. A report on blood and breath analyses of human subjects experimentally exposed to toluene and methyl ethyl ketone was prepared. Urinary excretion of m-methyl hippuric acid by workers exposed to xylene was studied. A project protocol was developed and a peer review held on a project to develop biologic monitoring techniques for occupational exposures to asphalts and coal tar pitches. (CONTACT PERSON: Dr. L. Lowry)

FY 1985 PROGRAM PLANS

Distribution and metabolism studies will be initiated on diglyme (bis [2-methoxyethyl] ether). Rats and mice will be orally dosed with $[^{14}\text{-C}]$ labeled compound and urinary metabolites separated by HPLC and identified by mass spectrometry. (CONTACT PERSON: Dr. F. Daniel)

Analytical methods will be investigated for urinary metabolites of compounds present in asphalts and coal tar pitches with the end point of the project being a biologic monitoring method for evaluating workers exposed to these materials. (CONTACT PERSON: Mr. W. Tolos)

Procedures for biologic monitoring of workers exposed to MEK, hexane, methylene dianiline, glycol ethers, and M-DEET (an insect repellant) will be completed and evaluated using specimens collected from exposed humans or animals. The results of the interlaboratory study of an MBOCA analytical method in urine will be published. (CONTACT PERSON: Dr. L. Lowry)

NCTR

FY 1984 ACCOMPLISHMENTS

Metabolism Section

Gentian Violet -- An improved method of extraction of $[^{14}C]$ gentian violet metabolites to achieve high recovery of total radioactivity has been developed and applied to rodent tissues. A variety of metabolites have been detected in various tissues including gentian violet and leuco gentian violet. Only the reduced leuco derivatives have been found to accumulate in fatty tissue, which contains the highest residue level in rats and mice.

A second analytical high performance liquid chromatography system using a reversed phase column and alkylsulfonate as an ion-pairing reagent has been developed and applied to tissue-extracts to complement the methanol-phosphate system in general use.

An intra species comparison has been made by dosing CD rats with $[^{14}C]$ gentian violet for one week. The total residue in various tissues was comparable to the results obtained with Fischer 344 rats, including the sex differences observed for the greater accumulation in fatty tissue in females.

In addition, pregnant female CD rats were dosed with $[^{14}C]$ gentian violet under the same treatment schedule as that for a teratogenesis study. In this case preliminary results indicate the fetus contains the lowest residue of all tissues sampled. There were significantly lower residue levels in fat of pregnant as compared to non pregnant female CD rats. (CONTACT PERSON: Dr. J. J. McDonald).

Sulfamethazine -- All work on the metabolism of sulfamethazine in swine that was conducted through an interagency agreement at the Metabolism and Radiation Research Laboratory of the USDA in Fargo, North Dakota, has been completed. All progress reports have been submitted and are being integrated into a comprehensive final report.

The triazene derivative of sulfamethazine, a possible product known to result from interaction of the drug with nitrite, has been synthesized and tested in two *Salmonella* strains for mutagenicity with negative results. The diazonium ion derivative, the precursor of the triazene, has been synthesized for mutagenicity and metabolism tests.

In vitro studies of the biotransformation of sulfamethazine with noninduced rat and mouse liver microsomes and induced rat liver microsomes were begun.

A preliminary feeding study to determine residue levels of $[^{14}C]$ sulfamethazine in rat tissues was done to determine the most useful concentration for chronic administration in the residue study. It was determined from the total residue of $[^{14}C]$ sulfamethazine metabolites in tissues that an aqueous solution of the labeled drug will be administered to rats and mice three times a day in an amount calculated to be 100 ppm in the diet. (CONTACT PERSON: Dr. J. J. McDonald).

FY 1985 PROGRAM PLANS

Gentian Violet -- Residue extraction and metabolite identification and quantitation in rodents will be completed. Final reports will be prepared for rodent and chicken residue studies.

The involvement of intestinal microflora in the metabolism of gentian violet will be continued by comparing metabolites in tissues from gnotobiotic rats with those from conventional rats. Metabolism of $[^{14}C]$ leuco gentian violet will be studied *in vivo* and *in vitro*.

Measurement of the mutagenicity of gentian violet metabolites in various test systems is being initiated.

Sulfamethazine -- It is anticipated that the major residue study in rodents will be completed in FY 1985.

CHEMICAL PATHOLOGY

NIEHS

The Chemical Pathology Branch is responsible for monitoring the quality of all aspects of anatomic and clinical pathology associated with studies conducted at NIEHS under the auspices of the National Toxicology Program (NTP). In addition, the Branch provides histology, electron microscopy, and collaborative support to the Intramural Research Program (IRP) of the NIEHS. The Branch's research efforts are directed toward evaluating and developing short-term *in vivo* carcinogenesis assays and characterizing and defining specific lesions observed in prechronic and chronic studies. The Branch is composed of four integrated Sections: Tumor Pathology, Toxicologic Pathology, Experimental Pathology, and Histology and Electron Microscopy.

Tumor Pathology Section

The Tumor Pathology Section assures that the pathology evaluation of the chronic NTP animal studies is precise, accurate, and state-of-the-art. The major emphasis in the past year has been on improving the quality of histological sections, standardizing tumor nomenclature and establishing uniform criteria for classification of neoplasms.

Increased effort is being made to assure that both tumor and nontumor diagnoses in the two-year studies are consistent and uniform between groups. This is especially important in detecting increased incidence or severity of a naturally occurring lesion. A data review prior to the quality assurance review has been instituted for early detection of data inconsistencies. Program pathologists participate in Pathology Working Group (PWG) reviews and two-year studies to gain a greater understanding of the goals of the Program.

FY 1984 ACCOMPLISHMENTS

Chronic Pathology Studies Reviewed -- During FY 1984, pathology reviews of 30 chronic studies (rats and mice) were held (Table 16). Each chronic study was given a quality assurance (QA) evaluation by an independent contract pathology laboratory. This included evaluation of the histotechnique, verification of computer tables with the original animal data records, verification of slide and tissue counts, and the initial pathology evaluation of all target tissues and all tumors. The QA report, with a list of differences of diagnostic opinion between the QA pathologist and the original pathologist, was sent to the Head of the Tumor Pathology Section who reviewed the report and selected members for a Pathology Working Group (PWG). The PWG chairperson reviewed the report slides, selecting representative slides for the PWG review. A PWG consists of four to six pathologists, some of whom are selected because of research experience with lesions peculiar to the bioassay being evaluated. The PWG members independently evaluate, in a blind fashion, those slides where diagnostic differences of opinion occurred and attempt to arrive at a consensus diagnosis. If the consensus diagnosis is different from that of the initial pathologist, the appropriate slides are returned to the initial pathologist for re-evaluation. The initial pathologist's re-evaluation becomes the final data of record. However, if it is significantly different from the PWG consensus, an additional set of pathology data may be included in the NTP Technical Report to reflect the PWG opinion. In most cases this is not necessary.

The PWG also has the responsibility of determining the overall quality of the histotechnique and the initial pathologist's evaluation. If an undue number of deficiencies are noted, the study may be considered inadequate and a partial or complete pathology re-evaluation may be required before acceptance by the NTP.

During FY 1984 all new pathology data were reviewed prior to submission of slides by the contract laboratory. The review included assessing: terminology/typography duplications and inconsistencies, positive and negative trends that may be chemically related, control tumor rates that are not within historical ranges, gross lesions not having corresponding microscopic diagnoses, and the animal data records for entries that were incorrect or did not meet GLP specifications.

If few or no problems are found, the study proceeds to QA; otherwise, the data is returned to the laboratory for further work. When the study is returned, the data is again subject to a pre-QA data review. This procedure is resulting in data that will better meet GLP standards and is increasing awareness in the laboratories of the need for precise data. (CONTACT PERSON: Dr. G. A. Boorman)

Pathology Data Audits -- In the summer of 1983, post-study data audits were instituted on all NTP studies coming to peer review. The raw data from each study is reviewed by an audit team consisting of toxicologists, chemists, and pathologists. The audit team is composed of NTP and contract personnel. The audit report is reviewed by NTP pathologists before a final report is issued. The chemicals that have been audited through the end of FY 1984 are shown in Table 17. Problems uncovered during this indepth review of the data have resulted in increased awareness of procedures necessary to avoid problems. This has resulted in modification of site visit procedures. (CONTACT PERSON: Dr. G. A. Boorman)

Tumor Nomenclature and Criteria -- During the past two years almost 200 naturally occurring brain tumors in the F344 rat have been reviewed and studied by Dr. Henk Solleveld. The studies included a variety of histological stains performed in collaboration with Duke University (Dr. Bigner) including immunoperoxidase stains for neurological markers (GFAP and S-100). The culmination of this study was an international symposium on Brain Tumors in Man and Animals held September 5-6, 1984. A study set of classifications of brain tumors in rats is being prepared. (CONTACT PERSON: Dr. G. A. Boorman)

Special Research in Rodent Pathology -- Dr. Katsuhiko Yoshitomi, NIH Guest Researcher from Osaka, Japan, is involved in studying the problem of increased incidences of subcutaneous tumors in male B6C3F1 mice. The historical incidence of subcutaneous tumors in mice in the NTP program is less than six percent in two-year studies, but in the control groups for several recent studies there have been incidences of tumors greater than twenty percent. The study involves further classification of these tumors and reviews to find common factors between studies with high tumor incidences. (CONTACT PERSON: Dr. G. A. Boorman)

Proliferative Pancreatic Lesions in F344 Rats -- The pancreata from over 2,000 F344 rats have been reviewed and the data accepted for publication. Proliferative pancreatic lesions are more common in rats receiving corn oil as a vehicle. The pathogenesis of this association is unknown and a Request for

Cooperative Agreement Applications (RFA) has been issued. It is the intent of the Chemical Pathology Branch in collaboration with investigators experienced in pancreatic carcinogenesis to explore the role of dietary oil in pancreatic cancer. (CONTACT PERSON: Dr. G. A. Boorman)

Myelotoxicity/Immunotoxicology -- In collaboration with the scientific staff of the NIEHS/NTP Immunotoxicology Section, the Tumor Pathology Section provided pathology support and myelotoxicity evaluation for several mouse studies. Myelotoxicity evaluation included bone marrow cellularity, pleuripotent stem cell assays (CFU-S), macrophage granulocyte assays (CFU-GM) plus a measure of erythropoiesis (Fe^{59} uptake). In addition to screening chemicals for myelo/immunotoxicity, efforts included methods development for evaluating and understanding mechanisms of myelotoxicity.

Mice exposed to chrysotile asbestos had depressed bone marrow parameters at 2, 12, and 26 weeks following a three-day exposure. While myelotoxicity has not been widely recognized in asbestos patients, there is evidence that Canadian miners exposed to asbestos have depressed circulating leukocytes possibly due to myelotoxicity. In vitro exposure of pulmonary macrophages to asbestos results in prostaglandin E (PGE) release which has a known negative feedback on the bone marrow. According to these studies the mouse model may prove useful in characterizing the nature of the immune dysfunction that has been reported to occur in asbestos exposed patients. By nine months post exposure mice are developing leukopenia. These results were published in 1984.

The subchronic (90-day) bioassay results of the NTP chemical ochratoxin suggested a degree of bone marrow hypocellularity consistent with myelotoxicity. To better characterize this effect, ochratoxin was included in the immunotoxicology program. In this study ochratoxin was shown to depress hematopoietic stem cell proliferation and antibody plaque forming cell response. These results were published in 1984. (CONTACT PERSON: Dr. G. A. Boorman)

The Myelotoxicity of Dioxin in DBA and B6C3F1 Mice -- It has been shown that sensitivity to myelotoxicity varies with the genetic background of the mice. Reciprocal transfers of treated resistant cells into sensitive hosts and vice versa has shown that dioxin myelotoxicity appears to reside with the bone marrow cells and not host factors. Findings are being compared with results for other immune parameters by the Immunotoxicology Section. These studies are still in a preliminary state but appear to offer an opportunity to explore the role of genetic factors in dioxin induced myelotoxicity. (CONTACT PERSON: Dr. G. A. Boorman)

Toxicologic Pathology Section

The Toxicologic Pathology Section assures the quality of pathology from acute, prechronic, and interim sacrifice studies in mice and rats, establishes diagnostic nomenclature for toxicologic pathology, and defines organ specific toxic lesions.

FY 1984 ACCOMPLISHMENTS

Prechronic Pathology Studies Reviewed -- During FY 1984, 25 prechronic studies were reviewed by the Toxicologic Pathology Section (Table 18). Studies are first reviewed through the quality assessment (QA) contractor. Attention is given to quality of histotechnique, tissue counts, slide inventory, accuracy of diagnoses, missing chemically induced lesions or target organs, and dosage recommendations for subsequent studies. The QA pathologist reviews all slides from six randomly selected animals sacrificed at the termination of the study from the highest dose groups with at least six survivors and six randomly selected controls from each sex. All slides are reviewed from all animals that are moribund sacrificed or die prior to termination of the study. All identified target organs are reviewed in all subsequent lower doses until a no-effect level is established. All tumors are reviewed. These findings are reviewed by the Section Head, and a Pathology Working Group (PWG) chairperson is assigned. The chairperson reviews pertinent slides and identifies discrepancies in diagnosis between the original pathologist and the QA pathologist. The PWG, consisting of four to six pathologists, reviews all differences of opinion in diagnoses, evaluates target organ effects, correlates clinical signs, significant abnormalities in clinical pathologic parameters, and differences in body and/or organ weights with morphologic changes, and makes dosage recommendations to the chemical manager based on pathologic data. The PWG also evaluates the quality of work performed by the original pathologist, QA pathologist and the histotechnique at the contracting laboratory. A summary report of these findings is written by the PWG chairperson and action items are returned to the original pathologist for reconsideration. This extensive review of prechronic toxicologic studies has resulted in a better understanding of chemically induced lesions in the host, target organ interactions, and has established a baseline for spontaneously occurring lesions in 19-to 22-week old Fischer rats and B6C3F1 mice. More emphasis has been put on definition and classification of non-neoplastic toxic lesions. NTP analysis of these studies has also provided a mechanism for monitoring contract laboratory work performance. (CONTACT PERSON: Dr. C. A. Montgomery)

Pathology Review of Interim Sacrifice Studies -- Approximately two years ago the NTP made a firm commitment to collect toxicologic data inclusive of anatomic pathology at 15 months into a two-year study. This time interval was chosen because there is a dramatic increase in tumor incidence in mice and rats at approximately 18 months into a study. The goal was to evaluate the clinical and anatomic pathology manifestations of chronic toxic injury before they are masked by concurrent neoplastic disease. The Toxicologic Pathology Section reviewed 21 of these interim sacrifice studies in FY 1984 (Table 19). Some of these studies had interim sacrifices at earlier intervals (3, 6, 9, or 12 months) and some had multiple sacrifices designed into the study. The data is reviewed like that described under the prechronic study section above. In addition to allowing pathogenesis studies of toxic lesions, these interim sacrifice evaluations present the opportunity to study early development of neoplastic lesions, and document end-points for time-to-tumor information. This additional responsibility for the Toxicologic Pathology Section doubled the PWG workload for the Section in FY 1984 resulting in less time for independent research. (CONTACT PERSON: Dr. C. A. Montgomery)

Pathology Data Base for Prechronic Studies -- In the past, 90-day prechronic studies have not been entered in the computerized Carcinogenesis Bioassay Data

System (CBDS) for data retrieval purposes. Prechronic pathology data are being collected utilizing the Toxicology Data Management System (TDMS) (described below). Retrospective pathology data captured on CBDS pathology forms are being evaluated by experienced rodent pathologists and a Compound Information Summary Sheet (CISS) prepared for each prechronic study. The data on CISS includes a summary of dosage information as well as mortality, clinical signs, organ weight, body weight, and clinical pathology data. Significant gross and microscopic lesions are recorded and target organs identified. Specific goals of this project include establishment of incidence rates for chemical target organs, correlation of organ weights and morphologic changes, determination of strain and species specificity for target organ effect, and investigation of dose setting criteria for two-year chemical studies. Twenty-five prechronic studies were evaluated during FY 1984 (Table 18). (CONTACT PERSON: Dr. C. A. Montgomery)

Toxicology Data Management System (TDMS) -- The TDMS has been implemented at nine of the NTP contract laboratories and two interagency agreement sites. Through FY 1984, 62 chemical studies have been put on this computer data base. The pathology nomenclature system is designed to use base terms, e.g., inflammation, degeneration, pigment, with qualifiers. All appropriate diagnoses are given a grade of severity. This consistency in terminology allows NTP to compare pathology data from different laboratories and compile meaningful information on lesion incidence. Several new software enhancements were added in FY 1984. TDMS now has the capability to accurately correlate gross and microscopic lesions and to account for significant anatomic sites in organs required for study by NTP, e.g., adrenal medulla, forestomach. Individual animal and organ summary reports have been improved. Versions 2.3 and 3.0 of the pathology software are presently under development. (CONTACT PERSON: Dr. C. A. Montgomery)

FY 1985 PROGRAM PLANS

Modification of the TDMS Pathology Code Table (PCT) -- The NTP has been using the Toxicology Data Management System (TDMS) for pathology data collection for three years. The last major PCT changes were implemented approximately eighteen months ago. A select group of pathologists, pathology technicians and computer data clerks met in the fall of 1984 to review the gross and microscopic pathology nomenclature for TDMS and made additions and/or deletions to the Pathology Code Table (PCT). (CONTACT PERSON: Dr. C. A. Montgomery)

Special Pathology Techniques -- The Chemical Pathology Branch is presently establishing a special pathology laboratory which will develop the capabilities for immunoperoxidase staining, muscle histochemistry, special bone pathology, soft plastic capabilities for thin section analysis of kidney, liver, and other target organs, and neuropathology inclusive of teased nerve preparations, morphometric analysis, and electron microscopy. Since these sophisticated techniques are often too difficult to perform on a large scale at NTP contract laboratories, the Chemical Pathology Branch's special pathology laboratory will develop methods and either perform the procedures in-house or standardize methods and instruct the laboratories on how to perform these studies. (CONTACT PERSON: Dr. C. A. Montgomery)

Experimental Pathology Section

The Experimental Pathology Section develops and validates animal models for chemical toxicity and carcinogenicity, investigates the pathogenesis of lesions observed in toxicity and carcinogenicity studies, and develops and standardizes clinical pathology procedures for use in rodent studies.

FY 1984 ACCOMPLISHMENTS

Hepatocarcinogenesis Research -- A study is currently under way utilizing a short-term rat liver tumor model to investigate the 2-hit hypothesis of carcinogenesis. Following a single intraperitoneal dose of diethylnitrosamine (DEN), the population of initiated hepatocytes is expanded by promotion for two months with dietary phenobarbital. After a second dose of DEN, an expanded population of cells with prior initiation (1st-hit) will be available for a second initiation (2nd-hit) ultimately resulting in a greater production of liver neoplasms, if the 2-hit hypothesis of carcinogenesis is operative. Stereologic measurements of phenotypically altered (gamma-glutamyl transpeptidase positive) preneoplastic foci will be made in addition to documentation of hepatocellular neoplasms. Initial studies were inconclusive and current plans are to repeat this experiment using neonatal rats. (CONTACT PERSON: Dr. R. R. Maronpot)

Short-term Rat Liver Tumor Model Studies -- Three contracts were awarded to refine the Peraino (one-day-old rat) or Pitot liver tumor models. Once refined, these models will be utilized to assess the relative initiating and promoting activities of rodent hepatocarcinogens. Model refinement took place during FYs 1983 and 1984 and included definition of dose response to several initiators and promotors, comparison of standard versus purified diet on liver tumor response, determination of sex differences in responsiveness of model, comparison of different routes of chemical administration on response, and characterization of potential indicators of neoplasia (histochemically altered foci) in the livers of treated rats. (CONTACT PERSON: Dr. R. R. Maronpot)

Short-Term Rat Urinary Bladder Tumor Model Studies -- A pilot study to establish a rat urinary bladder initiation-promotion model using an intravesicular injection of N-methyl-N-nitrosourea (MNU) as initiator and sodium cyclamate in drinking water as a promotor was completed and did not produce bladder tumors within the 9-month study period. (CONTACT PERSON: Dr. R. Melnick)

Strain A Mouse Pulmonary Tumor Validation Study -- The strain A mouse pulmonary tumor bioassay system was used to test 60 chemicals to determine how results of this short-term bioassay compared with results of rat and/or mouse conventional two-year carcinogenicity studies. The preliminary conclusion that the strain A mouse test system would not identify most of the chemicals found carcinogenic in the conventional two-year studies was confirmed. Further comparisons of strain A test results with organ-specific carcinogenic responses in the two-year studies and with genotoxicity test results were made late in FY 1983. Comparison of strain A mouse test results from two independent laboratories testing the same 25 chemicals indicates poor interlaboratory agreement. A manuscript is in preparation. (CONTACT PERSON: Dr. R. R. Maronpot)

Clinical Pathology Studies -- Liver function tests and isoenzyme measurements that are sensitive and specific to rodents are being investigated and refined. Specific tests under investigation include BSP and indocyanine green clearance, glutamate dehydrogenase and bile acid measurements on serum, and LDH isoenzyme measurements. (CONTACT PERSON: Dr. M. B. Thompson)

In Vivo Nuclear Magnetic Imaging and Spectroscopy on Rodents -- Rats treated with chemicals that produce specific organ damage or tumors are currently being studied by NMR imaging in collaboration with Duke University and NIEHS Intramural Research Program scientists. Initial results with a large bore human magnet are encouraging. Ultimately, a specific magnet for use on laboratory animals will be employed. (CONTACT PERSON: Dr. M. B. Thompson)

Study of Chemically Induced and Spontaneous Tumors for Oncogene Activity -- Spontaneous and chemically-induced tumors collected from the NTP chronic studies plus tumors obtained from in-house animal tumor models are being characterized pathologically and examined for the presence of transforming gene activity. This multidisciplinary effort is being done in collaboration with Dr. M. Anderson of NIEHS. Initial oncogene work is being conducted at the NIH in Dr. S. Aaronson's laboratory. (CONTACT PERSON: Dr. R. R. Maronpot)

Histology and Electron Microscopy Section

The Histology and Electron Microscopy Section is primarily a support facility serving the NIEHS Intramural Research Program (60%) and Toxicology Research and Testing Program (40%). The histology laboratory provides basic cutting and staining services and has limited capability for special stains and techniques. The electron microscopy laboratory also provides routine cutting and staining services. In addition, it provides technical help in the use of electron microscopy and interpretation of these observations.

FY 1984 ACCOMPLISHMENTS

During FY 1984 the histology laboratory supported 53 NIEHS scientists. In pursuing this effort, the laboratory sectioned and stained a total of 55,192 blocks of tissues. The electron microscopy laboratory supported 20 NIEHS scientists in their needs for ultrastructural examination of animal materials. (CONTACT PERSON: Mr. F. A. Talley)

OTHER FY 1984 CHEMICAL PATHOLOGY BRANCH ACCOMPLISHMENTS

The Chemical Pathology Branch developed a protocol which will significantly reduce the amount of microscopic pathology required on future chronic studies. The previous procedure required that 42 sections from 32 tissues be examined microscopically from all animals that died during the study and from those that survived the 104-week treatment period. Analyses of the results from previous NCI and NTP long-term studies indicated that significant reductions in the number of tissues examined could be implemented without compromising the ability to detect chemically-induced tumors. Further, the quality of the toxicologic pathology could be markedly improved through examination of some animals at a time period earlier than 24 months, when normal aging lesions often interfere with the detection and interpretation of chemical related lesions. Details of this protocol were described in last year's report. This protocol has been implemented on all new chronic studies started by the NTP in FY 1984. After two years, the protocol will be evaluated for its effectiveness. The incorporation of an interim evaluation at 15 months to define chronic toxicity was implemented in FY 1983. (CONTACT PERSON: Dr. E. E. McConnell)

Tumor Combination and Interpretation Guidelines -- Uniform guidelines for combining and interpreting tumors which occur in chronic tests were established in FY 1983 based upon input from Program pathologists and the NTP Board of Scientific Counselors. For specific organs where there is clear evidence of tumor progression, benign and malignant tumors will be counted separately for statistical purposes but they may be combined to more clearly delineate the carcinogenic potential of a given chemical. Guidelines for tumor combination will also be establisned for biologically similar tumors that occur in the same organ, such as fibromas and fibroadenomas of the rat mammary gland. Similarly, guidelines for documenting tumor multiplicity in a given organ and in paired organs were established. Non-neoplastic proliferative lesions (hyperplasia) are also included where differentiation between hyperplasia and neoplasia is difficult, particularly when this adds to the biologic interpretation of the lesion. (CONTACT PERSON: Dr. E. E. McConnell)

FY 1985 CHEMICAL PATHOLOGY BRANCH PROGRAM PLANS

Pathology Review and Workshop Activities -- In FY 1985 Quality Assurance and Pathology Working Group functions will be continued for prechronic and chronic tests to maintain a uniformly high quality of pathology for the Program. This workload will continue at FY 1984 levels through FY 1985.

Interlaboratory Variability in the Diagnosis of Neoplasms -- During FY 1985 investigations will continue to determine the cause of the significant variability in the incidence of certain neoplasms in both rats and mice between different contract laboratories. (CONTACT PERSON: Dr. E. E. McConnell)

Bioavailability of TCDD (Dioxin) from Soil -- The Chemical Pathology Branch is continuing its study on the bioavailability of 2,3,7,8,-tetrachlorodibenzo-p-dioxin in soil using the guinea pig model. The results of this study should allow one to make a more accurate analysis of the health hazard associated with living in such a contaminated environment. (CONTACT PERSON: Dr. E. E. McConnell)

Fibrogenicity and Carcinogenicity of Wollastonite -- Wollastonite, a natural fibrous mineral, has been proposed as a substitute for asbestos in certain applications. Because of this, an inhalation study in F344 rats was started in FY 1983 and will be finished in FY 1986 to evaluate the fibrogenic and carcinogenic potential of the mineral using chrysotile asbestos as a positive control. Exposure is for either 12 or 24 months with interim sacrifices at 3, 12 and 24 months. The remaining rats will be allowed to live out their natural life span. (CONTACT PERSON: Dr. E. E. McConnell)

Special Pathology Techniques -- The Chemical Pathology Branch is developing the in-house capability to perform immunoperoxidase stains on spontaneous and induced rodent tumors. While initial attempts with keratin stains have been successful, collaborative efforts through Clement Associates and the University of North Carolina (Dr. V. Gillespie, Department of Neurosurgery) will be used to validate this technique for pancreatic islet cell tumors and central nervous system tumors. It is expected that identification of antigens on induced tumors in two-year studies will be used frequently to aid in the interpretation of these studies.

NTP PATHOLOGY ARCHIVES

The NTP maintains a centralized archives of histopathology materials collected during the bioassay studies. This is done in accordance with Good Laboratory Practice procedures and to provide a complete history of the pathology findings. Storage facilities are provided for wet tissues, paraffin blocks, microscopic slides, and printouts of the data that appear in the technical reports. User facilities complete with microscopes are provided for investigators to view the materials. During the first quarter of FY 1985, the NTP pathology archives were being moved from Rockville, Maryland to Research Triangle Park, North Carolina. For more information or scheduling of user facilities, contact Dr. G. A. Boorman, Acting Chief, Chemical Pathology Branch, National Toxicology Program, P. O. Box 12233, Research Triangle Park, NC 27709; or call (919) 541-3440 (commercial), 629-3440 (FTS).

TABLE 16

CHRONIC STUDIES REVIEWED DURING FY 1984

	CAS No.
Ampicillin Trihydrate	7177-48-2
Benzene (rats and mice, hematology review)	71-43-2
Benzyl Acetate (mice, special review)	140-11-4
Bromodichloromethane (mice)	75-27-4
n-Butyl Chloride (mice)	109-69-3
Chlorendic Acid	115-28-6
Chloroform II (EPA)	67-66-3
3-Chloro-2-Methylpropene	563-47-3
Chlorowax 40 (mice and rats)	51990-12-6
Chlorowax 500C (rats)	63449-39-8
C.I. Disperse Blue 1	2475-45-8
Cyclohexanone (mice)	108-94-1
Decabromodiphenyl Oxide	1163-19-5
p-Dichlorobenzene (mice)	106-46-7
Diesel Fuel Marine (mice)	
Dimethyl Methyl Phosphonate (mice)	756-79-6
Ephedrine Sulfate	134-72-5
Ethylene Glycol Monoethyl Ether	110-80-5
8-Hydroxyquinoline (female mice, special review)	148-24-3
Malonaldehyde (mice)	542-78-9
Navy Fuel JP-5 (mice)	
o-Phenylphenol (mice)	90-43-7
Propylene Oxide (NIOSH)	75-56-9
Styrene Oxide	96-09-3
Tetrachloroethylene (mice)	127-18-4
1,1,1-Trichloroethane (Methylchloroform) (mice, special review)	71-55-6
Trichloroethylene (special review)	79-01-6
4-Vinylcyclohexene	100-40-3
4-Vinylcyclohexene (female mice, special review)	100-40-3
Xylene (rats)	1330-20-7

TABLE 17

COMPLETED DATA AUDIT REVIEWS

THROUGH FY 1984

Chemical	CAS No.
Ampicillin Trihydrate	7177-48-2
Asbestos Chrysotile (rats)	12001-29-5
Benzene	71-43-2
Benzyl Acetate	140-11-4
1,3-Butadiene	106-99-0
Butyl Benzyl Phthalate	85-68-7
n-Butyl Chloride	109-69-3
Chlorinated Trisodium Phosphate	56802-99-4
Chlorodibromomethane	124-48-1
2-Chloroethanol	107-07-3
3-Chloro-2-Methylpropene	563-47-3
C.I. Basic Red 9	569-61-9
C.I. Disperse Blue 1	2475-45-8
Diallyl Phthalate	131-17-9
1,2-Dichlorobenzene	95-50-1
p-Dichlorobenzene	106-46-7
Dichloromethane (Methylene Chloride)	75-09-2
1,3-Dichloropropene (Telone II)	542-75-6
Di(2-ethylhexyl)phthalate	117-81-7
Dimethylhydrogen Phosphite	868-85-9
Dimethyl Morpholinophosphoramidate (DMMPA)	597-25-1
Dimethylvinyl Chloride (DMVC)	513-37-1
Ethylene Dibromide	106-93-4
Ethylene Glycol Monoethyl Ether	110-80-5
Glutaraldehyde	111-30-8

TABLE 17 (Continued)

Chemical	CAS. No.
Hamamelis Water (Witch Hazel)	68916-39-2
H.C. Blue 1	2784-94-3
H.C. Blue 2	33229-34-4
H.C. Red 3	2871-01-4
8-Hydroxyquinoline	148-24-3
Isophorone	78-59-1
Malonaldehyde	542-78-9
Mirex	2385-85-5
Propylene	115-07-1
Propylene Oxide	75-56-9
Pyridine	110-86-1
Sodium Dodecyl Sulfate	151-21-3
Tetrachloroethylene (mice)	127-18-4
Tetrachloroethylene (rats)	127-18-4
Toluene Diisocyanate	26471-62-5
1,1,1-Trichloroethane	71-55-6
Trichloroethylene	79-01-6
Tris(2-ethylhexyl)phosphate	78-42-2

TABLE 18

PRECHRONIC STUDIES REVIEWED DURING FY 1984

Chemical	CAS No.
Acetonitrile	75-05-8
Barium Chloride Dihydrate	10326-27-9
O-Benzyl-p-Chlorophenol	120-32-1
2,2-Bis(Bromomethyl)-1,3-Propanediol	3296-90-0
Caffeine	58-08-2
C.I. Direct Blue 218	28407-37-6
Dimethyloldihydroxyethylenurea	1854-26-8
Doxylamine	469-21-6
Isobutyl Nitrite	452-56-3
Isobutyraldehyde	78-84-2
Methdilazine	1982-37-2
Methyl Bromide	74-83-9
Molybdenum Trioxide	1313-27-5
p-Nitroaniline	100-01-6
p-Nitrotoluene	99-99-0
Promethazine Hydrochloride	58-33-3
Propantheline Bromide	50-34-0
Psoralen IV	
Thenyldiamine	91-79-2
Triamterene	396-01-0
1,2,3-Trichloropropane	96-18-4
Tricresyl Phosphate	1330-78-5
Tripelennamine	91-81-6
Tumeric Oleoresin	8024-37-1
Vinylidene Fluoride	75-38-7

TABLE 19

INTERIM SACRIFICE STUDIES REVIEWED DURING FY 1984

Chemical	CAS No.
t-Butyl Alcohol - 3 months	75-65-0
t-Butyl Alcohol - 6 months	75-65-0
t-Butyl Alcohol - 12 months	75-65-0
α-Chloroacetophenone - 15 months	532-27-4
C.I. Direct Blue 15 - 9 months	2429-74-5
2,4-Diaminophenol-Dihydrochloride- 15 months	137-09-7
Dimethoxane - 15 months	828-00-2
3,3'-Dimethoxybenzidine - 9 months	119-90-4
Epinephrine Hydrochloride - 15 months	55-31-2
Furan - 3 months	110-00-9
Furan - 9 months	110-00-9
Furan - 15 months	110-00-9
H.C. Yellow 4 - 6 months	52551-67-4
Hydrochlorothiazide - 12 months	58-93-5
4-Hydroxyacetanilide - 15 months	103-90-2
Methyl Carbamate - 18 months	598-55-0
Ochratoxin A - 9 months	303-47-9
Ochratoxin A - 15 months	303-47-9
Quercetin - 6 months	117-39-5
Quercetin - 15 months	117-39-5
Sodium Fluoride - 12 months	7681-49-4

CUTANEOUS TOXICOLOGY

The likelihood of the skin being exposed to toxic chemicals is extremely high--it is exposed in the occupational setting, while using chemicals at home, and to a wide range of cosmetic and toiletry formulations and drugs in a variety of vehicles. These chemicals can damage the skin in many ways, and also many can be absorbed through the skin to produce toxic effects elsewhere in the body. Within the NTP, the potential of chemicals to produce skin irritation, sensitization, and tumors, and the ability of chemicals to be absorbed through the skin are being studied. Percutaneous absorption of toxic chemicals may affect reproduction, development, cancer formation and the functioning of various organ systems.

NTP is a member of the DHHS *Ad Hoc* Interagency Dermatology Working Group. Information from agencies outside of NTP is useful in planning future NTP research activities. Experts within and outside of NTP participate in peer review of projects and manuscripts. In addition, several groups representing industry and many individuals with interests in dermal testing and experimentation have been contacted for input into the NTP dermal testing effort. (CONTACT PERSON: Dr. W. Eastin)

NIEHS

FY 1984 ACCOMPLISHMENTS

Toxicity Testing Studies -- NTP develops chemical specific testing protocols designed to examine the toxicity by the most usual route of exposure to humans. Continual critical evaluation of testing procedures and of the test results of completed and ongoing studies is one method being used to improve and expand the design of future dermal tests. During the past year, completed skin exposure studies were used to revise the guidelines for performing dermal studies in the most recent (1984) Statement of Work. The ultimate goal is to establish the best design to test chemicals by dermal exposure using procedures which will maximize the chances of observing any toxic effects. NIEHS is presently evaluating the carcinogenic and toxicologic properties of ten chemicals following dermal exposure to rats and mice. (CONTACT PERSON: Dr. W. Eastin)

Initiation/Promotion Studies -- Some chemicals are identified as potential tumor promoters based either on results from long-term testing or on a structure activity relationship similar to a known promoter. For these chemicals, NTP may elect to examine this potential in one or more specialized tests. For the mouse skin initiation/promotion studies, a basic study design was recently prepared with the help of outside scientists to help provide more uniformity between these studies. This basic design is expanded to meet chemical-specific testing requirements. Data obtained from these tests provide additional information useful to the interpretation of the toxic potential of test chemicals. (CONTACT PERSON: Dr. W. Eastin)

Methods Development -- Methodology to obtain data on rates of dermal absorption, on effects of various vehicles on absorption, and on dermal metabolism in an *in vitro* system, is being evaluated. Information of this type will be used by chemical managers as an aid in the design of chemical-specific testing when the most usual route of exposure is dermal. (CONTACT PERSON: Dr. W. Eastin)

Psoralens -- Toxicity to the skin can also occur following ingestion or inhalation of a chemical and its subsequent localization in the skin. A good example of this is seen after oral administration of psoralens (P); the psoralen localizes in the skin and ultraviolet light (UVA) exposure to the skin causes a psoralen-DNA interaction and subsequent skin toxicity. The NTP is evaluating the toxicity of psoralens and UVA (PUVA) in the hairless mouse to aid in determining the toxic potential of PUVA therapy in humans, a therapy which has recently been approved for the treatment of psoriasis. It is estimated that approximately 3% of the United States population suffers from this disease. These animal studies are designed to look at the metabolism and toxic and carcinogenic properties of the psoralens. Studies in the hairless mouse have shown that maximum phototoxicity to psoralens (8-methoxypsoralen) results one and a half hours after oral administration, a time which correlates with peak skin levels of a psoralen. A study is now under way to determine tumor response after repeated psoralen and UVA light exposure. (CONTACT PERSON: Dr. J. Dunnick)

Flame Retardants -- The NTP is investigating the toxic and carcinogenic properties of a variety of flame retardants. A comparison of the oral and dermal toxicity of the flame retardant 2,2-bis(bromomethyl)-1,3-propanediol has shown that this chemical is more efficiently absorbed after oral than after dermal administration. (CONTACT PERSON: Dr. J. Dunnick)

On the other hand, flame retardants such as 2,3-dibromo-1-propanol are rapidly and efficiently absorbed dermally. The carcinogenicity of this chemical is now being studied by the NTP. (CONTACT PERSON: Dr. R. Melnick)

FY 1985 PROGRAM PLANS

Toxicity Testing Studies -- Efforts will continue to be focused on developing dermal test procedures to examine nominated chemicals in a manner most similar to normal human exposure. An established working relationship with groups outside of NIEHS and with individual scientists with interests in dermal studies will continue to be a source for advice on improving these tests.

Initiation/Promotion Studies -- Studies are planned to compare the responses of several mouse strains to known initiators and promoters and to establish baseline data on these chemicals. Information from these studies should assist in the selection of a mouse strain and of chemicals to use as positive controls for future studies. (CONTACT PERSON: Dr. W. Eastin)

Methods Development -- The establishment of the methodology for obtaining routine measurements on rodent skin *in vitro* will be continued. Goals are to rapidly obtain results on chemicals to establish limits of absorption of applied dose, and to examine the effects of vehicles on chemical absorption. This information will be provided for consideration in the design of *in vivo* toxicity testing. (CONTACT PERSON: Dr. W. Eastin)

NIOSH

FY 1984 ACCOMPLISHMENTS

Toxicity Testing Studies -- Final reports were prepared on the irritating (rabbits) and sensitizing (guinea pigs) properties of ethyl silicate, and of the sensitizing properties of acrolein and N,N-dimethylacetamide. Ethyl silicate at concentrations below 25% in corn oil was not irritating and at 15% it was not sensitizing, indicating little potential for irritation or sensitization in occupational use. Acrolein at a concentration of 0.0005% in distilled water and N,N-dimethylacetamide at 5% in distilled water were not sensitizing to guinea pigs, suggesting there would be low risk for allergic contact dermatitis in humans. (CONTACT PERSON: Dr. A. Susten)

Ethylene glycol monoethyl ether and ethylene glycol monomethyl ether acetate were teratogenic when tested by dermal application; ethylene glycol monobutyl ether and diethylene glycol monoethyl ether were not teratogenic by dermal application in the same study. (CONTACT PERSON: Dr. B. Hardin)

Absorption -- The *in vivo* method for directly quantitating the percutaneous absorption of volatile chemicals using hairless mice was made operational and absorption of benzene, benzene in rubber solvent, toluene, carbon disulfide and ethyl benzene were studied. For benzene and carbon disulfide, the absorption rates, 0.25 and 0.46 mg/CM^2/hr, respectively, were comparable to previously reported human data; for toluene, the rate of 0.45 mg/CM^2/hr was 1/40 of the rate previously reported for humans. The rate of absorption of benzene in rubber solvent was not notably different from the rate for neat benzene. The results of the benzene studies were submitted to the Occupational Safety and Health Administration in support of the occupational exposure standard for benzene. Data on ethylbenzene are being analyzed. (CONTACT PERSON: Dr. A. Susten)

Mechanical Trauma -- The proceedings of the workshop on mechanical trauma to skin are being prepared for publication in an industrial hygiene journal. (CONTACT PERSON: Dr. A. Susten)

FY 1985 PROGRAM PLANS

During FY 1985 the workshop proceedings on mechanical trauma to the skin should be published, as will data collected during FY 1984 on skin absorption. A study of percutaneous absorption of N,N-diethyl-m-toluamide is planned. Planning for a conference on issues related to dermal absorption in occupational settings will take place. (CONTACT PERSON: Dr. A. Susten)

IMMUNOLOGICAL TOXICOLOGY

Three classes of undesirable effects may occur when the immune system is perturbed by advertent (e.g. drugs) or inadvertent (e.g., environmental pollutants) exposure to chemicals and include: (1) those which result in immunodeficiency or suppression; (2) those which alter host defense mechanisms; and (3) those which induce hypersensitivity or allergy. Evidence of increased bacterial, viral, fungal and parasitic diseases in patients on chronic immunosuppressive chemicals has been well documented. Likewise, it has been observed that the incidence of cancer in organ transplant recipients on prolonged immunosuppressive chemotherapy greatly exceeds that which occurs in the general population. In another light, the increased incidence of hypersensitivity disease associated with exposure to certain chemicals in the workplace is well established.

Studies in laboratory animals support these clinical observations and demonstrate an enhanced incidence of UV-induced or benzo(a)pyrene-induced cancer in mice treated with immunosuppressive agents. The mechanisms and relationship between altered host resistance and immune dysfunction is complex, poorly defined, and of extreme importance to understand. Chemicals of environmental concern have been shown to induce immunosuppression as evidenced by altered antibody-mediated immunity, cell-mediated immunity, natural killer cell activity or macrophage function in rodents following sublethal exposure. Some examples of chemical immunotoxicants include asbestos, polyhalogenated aromatic hydrocarbons, diethylstilbestrol, polycyclic aromatic hydrocarbons, hexachlorobenzene, pentachlorophenol and certain organo and heavy metals. Studies have also indicated that exposure to certain chemicals can alter host resistance to bacteria, viruses, parasites and transplanted tumor cells.

Correlation of such immunological findings with altered host susceptibility and the extrapolation of these chemically-induced immunobiological effects to humans is of major concern to the NTP Immunological Toxicology Program. The Program systematically: (1) evaluates and examines the influence of selected environmental chemicals on the immune system that occurs following *in vitro* and *in vivo* exposure to chemicals; (2) relates alterations in immunological functions to both general toxicity as well as specific organ toxicity; (3) relates changes in immunological functions with altered host resistance following challenge with either syngeneic tumor cells or infectious agents; and (4) refines and validates a panel of immune and host resistance procedures in order to better define *in vitro* and *in vivo* immunotoxicity.

NIEHS

FY 1984 ACCOMPLISHMENTS

Immunotoxicology Screening Battery -- The NTP immunotoxicology contract laboratories, with assistance by the NIEHS intramural staff and the Immunology Section of the Chemical Industry Institute of Toxicology, have defined a screening panel for evaluation of chemicals with respect to their ability to alter immune functions and host resistance to challenge with infectious agents or tumor cells in mice (Table 20). This panel was selected following a comprehensive two-year study designed to develop improved methodology for measuring altered host resistance and immunological impairment in rodents exposed to chemicals of environmental concern. These efforts encompassed development, refinement and interlaboratory validation of the assay systems.

Screening Studies -- A number of compounds of specific interest to the NTP were examined in FY 1984 in this contract. In addition to validating the test systems, these studies have been used to increase the existing data base to be used for health-risk assessment. Compounds evaluated in FY 1984 and a summary of the results are shown in Table 21.

Basic Studies -- In-house research efforts have continued to focus on elucidation of general immunotoxic mechanisms. In order to accurately predict human health risk and no-effect levels, the mechanisms mediating immunotoxic reactions need to be more clearly defined.

Previous studies have clearly established that physiologic and pharmacologic levels of estrogens modulate immunologic responses that result in simultaneous activation of the reticuloendothelial system and depression of cell-mediated immunity. The mechanisms of estrogen immunoregulation were examined in mice administered pharmacologic levels of exogenous estrogens. Evaluation of steroidal and nonsteroidal compounds with varying degrees of estrogenicity (i.e., uterotrophic activity) provided evidence that their immunotoxicity, for the most part, correlated with estrogenicity. The mechanisms responsible for these effects appear to be complex, mediated through a direct chemical interaction with lymphoid target cells, as well as with nonlymphoid tissue, resulting in the release of soluble immunoregulatory factors. The latter phenomenon was examined in detail and it appears to constitute qualitative or quantitative changes in thymic hormones produced by thymic epithelium in response to an estrogen stimulus. Thymic hormones are required for T cell maturation. This response is not only estrogen specific but requires specific binding of the compound to estrogen receptors or receptor-like structures present in cytosol preparations from thymic epithelial cells. The biological relevance of these observations is being examined in a series of host infectivity models.

The immunological effects of benzidine (4,4'-diaminobiphenyl) were examined in B6C3F1 mice exposed by gavage to dose levels ranging from 50 to 200 mg/kg body weight. Suppression of cell mediated immune functions and natural killer cell activity predominated. The alterations associated with benzidine exposure were consistent with the idea that benzidine immunosuppression may act as a cofactor in promoting carcinogenesis in that immunosuppression by benzidine occurred at dose levels equal to or less than those which are carcinogenic; the suppression was relatively long lasting and was focused on those immune functions believed to be primarily involved in tumor immunity. In vitro studies with benzidine mimicked the suppression of lymphocyte responsiveness to mitogens observed in vivo, and further suggested that immunosuppression occurred as a result of alterations in the lipoxygenase pathway of arachidonic acid metabolism. This pathway is known to be involved in the response of the B cell to both mitogens and antigens, and benzidine is an effective cosubstrate for the hydroperoxidase enzyme activities, providing necessary reducing equivalents. Present studies are concerned with defining the mechanism of benzidine-induced suppression of lymphocyte responses. It is not known whether metabolites of benzidine are responsible for this suppression or if it is due to altered levels of the normal products of the lipoxygenase pathway, such as leukotrienes. These products are responsible for altering cellular levels of cyclic GMP, which normally increase during lymphocyte blastogenesis.

Mice were administered the anticonvulsant, diphenylhydantoin (DPH), by oral gavage at doses up to 200 mg/kg body weight from one to four weeks. None of the dosing regimens caused toxicological manifestations other than hepatomegaly at the highest dose level. Evaluation of the immune status of the drug-treated mice revealed no alteration of lymphocyte responsiveness to mitogens or cell-mediated immunity. Humoral immunity, as determined by serum immunoglobulin concentrations and plaque-forming cell responses, was depressed by DPH, as was host resistance to infection with the parasite, Plasmodium yoelii. The bone marrow was the most sensitive target with loss of the multipotent stem cell (CFU-S) occurring within one week. Depression of CFU-S colonies was selective in that loss of only cells in S phase occurred and thymosin, which alters cell cycle kinetics, protected against this effect. Committed granulocyte macrophage progenitor cells (CFU-GM) were inhibited by DPH in vivo as well as in vitro at concentrations as low as 2.5 x 10^{-7}M. Addition of thymic factors including supernatant from cultured thymic epithelial cells restored CFU-GM formation. Bone marrow cells from DPH-treated mice were folate deficient, as judged by the deoxyuridine suppression test. Administration of folic acid either in vitro or in vivo restored bone marrow functions.

Several immunological processes with defined stages of proliferation and differentiation are being used to study cellular changes associated with acute 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure in adult mice. Among the acute toxic effects that occur following in vivo TCDD exposure at dose levels of approximately 1 µg/kg body weight are suppression of antibody plaque forming cells in the spleen and numbers of granulocyte-macrophage colony forming units (CFU-GM) in the bone marrow. These alterations also occur following in vitro exposure of B lymphocytes or bone marrow cells to TCDD at concentrations as low as 10^{-9}M. Structure-activity and genetic studies indicate that these effects are most likely associated with the presence of a high affinity, stereospecific receptor normally found in the mouse liver. A receptor with similar characteristics was found to be present in cytosol from nucleated bone marrow cells of high responding ($Ah^{dd,db}$), but not low responding (Ah^{bb}) mice. In vitro studies employing long-term bone marrow cultures and leukemic cell lines suggested that TCDD selectively alters cellular differentiation processes. (CONTACT PERSON: Dr. M. Luster)

FY 1985 PROGRAM PLANS

The immunotoxicology contract laboratories will continue to examine selected chemicals for altered host resistance and immunological function using the standard protocol. Chemicals recommended for testing in FY 1985 include delta^9-tetrahydrocannabinol, ethylene dibromide, vinylcyclohexene diepoxide and 1,3-butadiene.

Intramural research will continue studies on the elucidation of mechanisms that mediate chemical-induced immunotoxicity. Experiments will focus on alterations in lymphocyte proliferation and differentiation induced by TCDD to ascertain the cellular events associated with TCDD toxicity.

In vitro studies with benzidine mimic the suppression of lymphocyte responses to mitogens observed in vivo. In vitro studies will be expanded to determine the role of the lipoxygenase pathway of arachadonic acid metabolism in immunosuppression by substrates used in co-oxidation. (CONTACT PERSON: Dr. M. Luster)

NIEHS co-sponsored an international conference on immunotoxicology held in Luxembourg on November 6-9, 1984. Other co-sponsors were the Commission of the European Communities, the International Programme on Chemical Safety of the World Health Organization, the United Nations Environment Program, the International Labor Organization, and the Environmental Protection Agency. (CONTACT PERSON: Dr. L. Moustafa)

TABLE 20

CORE PANEL FOR DETECTING CHEMICAL-INDUCED IMMUNOTOXICITY

Parameter	Procedure Performed
Infectivity Models	• Influenza or Streptococcal challenge: LD_{20} + LD_{80} challenge
	• Listeria monocytogenes challenge: LD_{20} + LD_{80} challenge
	• PYB6 tumor cell challenge: TD_{20} + TD_{80} challenge
Immunological Assays	• Natural killer cell activity
	• Antibody response to sheep red blood cells (SRBC)
	• Mixed leukocyte culture (MLC) response
	• Lymphocyte blastogenesis to mitogens
	• Enumeration of splenic B and T lymphocytes
Toxicology Evaluation	• Body weight and selected organ weights
	• Hematology
	• Selected serum chemistries
Macrophage Functions	• Peritoneal cell numbers and differential
	• Phagocytosis
	• Ectoenzyme levels

TABLE 21
CHEMICALS ASSESSED FOR POTENTIAL IMMUNOLOGICAL ALTERATIONS[a]

	Parameter Examimed				
Compound	B Cell Function	T Cell Function	Natural Killer Cell Activity	Macrophage Function	Host Resistance
Cadmium Chloride[a]	NE	↓	NE	↑	NE
Dimethylvinyl-chloride	↓	NE	NE	NE	↓
Pentachlorophenol (PCP)[b]	↓	NE	↑	NE	NE
Nitrobenzene[c]	NE	NE	NE	↑	NE
Benzidine[c]	NE	↓	↓	NE	↓

Symbols: ↓ - significantly decreased; ↑ - significantly increased; NE - no effect.

[a] Mice ($B6C3F_1$) were exposed to test compound for 14 consecutive days except $CdCl_2$ which was administered for 90 days.

[b] Only PCP contaminated with dibenzodioxin and dibenzofuran was immunosuppressive.

[c] These compounds caused severe myelotoxicity.

NEUROBEHAVIORAL TOXICOLOGY

Behavioral and neurologic alterations in response to environmental pollutants often represent the earliest manifestations of toxicity in animals. Thus, neurobehavioral test systems must be developed and chemicals must be tested for neurobehavioral effects.

The NTP neurobehavioral program involves the development, standardization, and validation of neurobehavioral screening tests. Such a test battery provides a general indication of the presence of neurotoxicity in terms of neurobehavioral functions that may be affected. Known representative neurotoxicants are studied using the test battery to determine the level of sensitivity and selectivity of each component test. This battery with continuing refinements is used as part of the general toxicology screen and in the prechronic phase of two-year toxicology and carcinogenesis testing. Additionally, there will be continuing development and evaluation of human neurotoxicity tests to be used at the worksite or in the laboratory.

An additional objective is the development of a test capability for more extensive indepth toxicological characterization of selected chemicals either identified in preliminary neurobehavioral screening or which are of public health concern including behavioral teratologic evaluation.

NIEHS

FY 1984 ACCOMPLISHMENTS

Basic Neurobehavioral Studies -- Organochlorine chemicals such as chlordecone, p,p'-DDT, and 1,2,3,4,5,6-hexachlorocyclohexane (lindane) are widely used in developing countries and to a lesser extent in some industrialized countries. To date, there have been several attempts to identify and describe the neurobehavioral effects of the organochlorines, but there have been no systematic attempts to develop an animal model of organochlorine neurobehavioral toxicity leading to study of their mechanisms of action. The purpose of this research is to characterize in an animal model the behavioral and neurological toxicity of chlordecone and study the mechanisms by which chlordecone and other organochlorine chemicals produce their neurotoxic effects.

A procedure developed at NIEHS has been used to quantify the effects of three organochlorine chemicals and permethrin, a pyrethroid insecticide believed to have a mechanism of action identical to that of p,p'-DDT. Previous work has shown that chlordecone-induced tremor can be differentiated from that produced by pharmacological agents such as harmine, oxotremorine, apomorphine or cold-induced shivering. Recent work has shown that the tremor produced by chlordecone can be differentiated from that of p,p'DDT and permethrin on the basis of spectral analysis of movement; lindane was found to produce convulsions not preceded by tremorigenic episodes. Mirex, an analogue of chlordecone, and o,p'-DDT were found to have little tremorigenic activity over a wide range of doses.

Pharmacological challenges consisting of psychoactive drugs (receptor antagonists and agonists, neurotransmitter releasers, etc.) and cytotoxicants (6-hydroxydopamine) have been used to study the role of various neurotransmitter systems in the mediation of chlordecone and p,p'-DDT-induced tremor. The results with both agents indicate that a single neurotransmitter system (i.e., serotonin, norepinephrine, GABA, acetylcholine) is not involved in the mediation of the tremor. Our studies do indicate that tremor appears to originate in the brain stem.

Current research is focusing on the neuropharmacological mechanism of organochlorine-induced tremor. 5,5-Diphenylhydantoin (dilantin), an anticonvulsant believed to block the repetitive neuronal discharges by acting at the sodium gate, was found to block the tremor and hyperexcitability produced by p,p'-DDT and permethrin; these agents are believed to increase neuronal excitability and produce repetitive discharge by holding sodium gates open once they are open. Dilantin, on the other hand, was found to potentiate the tremor produced by chlordecone, suggesting that this organochlorine produces tremor by a different mechanism.

Additional studies have been performed to quantify the effects of chlordecone and related insecticides on behavioral hyperexcitability as measured by the acoustic startle response. Dose- and time-effect experiments have been performed and the data indicate that chlordecone, p,p'-DDT, lindane and permethrin all augment the startle response. Preliminary analysis shows that each agent increases initial responsiveness (i.e., produces sensitization) and appears to attenuate or block subsequent habituation of the response to repeated presentations of the stimulus. (CONTACT PERSON: Dr. H. Tilson)

Neurobehavioral Test Methods Development -- Progress was made in the construction of a battery of domiciliary (home) cages that continuously monitor naturally occurring consummatory and motor activity behaviors of laboratory animals during exposure to chemicals. Each cage is equipped with photocells to detect movement in the home cage and touch-detectors for the remote sensing of eating and drinking behavior. Output from the sensors is connected to a laboratory computer that counts the frequency of homecage behaviors. Validation of the system was accomplished by demonstrating diurnal activity cycles and ingestive behavior; mild restriction of food resulted in the expected changes in activity and resumption of food availability produced robust changes in consummatory behaviors. Acute dose-response determinations for psychoactive drugs known to affect motor activity and ingestive behavior (d-amphetamine and scopolamine) also validated the reliability and sensitivity of the apparatus. Currently, studies on the effects of known neurotoxicants such as trimethyl tin and acrylamide are under way. (CONTACT PERSON: Dr. H. Tilson)

FY 1985 PROGRAM PLANS

Basic Neurobehavioral Studies -- Research on the tremorigenic effects of the organochlorines and permethrin will be continued. The possible role of calcium in the tremor produced by chlordecone and related agents will be studied using intracerebral injection procedures to deliver calcium ions, channel ionophores and blockers directly to the CNS.

Future studies will also attempt to determine the possible site of action of the tremor produced by these compounds. Recent experiments conducted in another laboratory have shown that direct administration of p,p'-DDT into brain stem sites produces myoclonia; injection into regions such as the hippocampus, cerebellum and caudate nucleus did not produce these effects. We propose to microinject small quantities of chlordecone and p,p'-DDT into various regions of the brain in an attempt to elicit tremor. Pharmacological challenges effective against tremor produced by systemic administration will then be employed against tremor produced by the central route.

The effects of chlordecone and related agents on the startle response will also be studied in greater detail. First, pharmacclogical challenges employed in studies on tremor (i.e., dilantin, calcium) will be used to study behavioral reactivity produced by these agents. Such studies will again test the assumption that the mechanism for behavioral hyperreactivity is the same as that for tremor. In addition, a series of studies is planned which will study the role of serotonin in the enhancement of the acoustic startle response.

Additional studies on the behavioral mechanism of organochlorine-induced hyperexcitability are planned. Work conducted in other laboratories has shown that sensitization is mediated at some point in the motor side of the startle reflex circuit, while habituation is effected by longer sensory motor pathways. We intend to determine the effects of chlordecone on sensitization and habituation in our laboratory. One prediction is that if chlordecone is a nonspecific neural toxicant, then it should affect the excitability of all components of the startle reflex. Thus, it should produce sensitization as well as attenuate habituation to repeated stimulus presentations.

Another feature of organochlorine-induced neurotoxicity is that there may be an activation of adaptive responses in the nervous system. This has been observed in studies on tremor in which some receptor populations (serotonin, alpha 2-noradrenergic) actually exacerbated the tremor produced by chlordecone. In addition, one of the common features of the neurobehavioral toxicity produced by these agents is behavioral hyperreactivity. These data suggest that one consequence of organochlorine exposure is a net alteration of processes that normally act to inhibit responding under some circumstances. Over the next year, we intend to initiate studies designed to evaluate the effects of chlordecone on responding under other conditions in which a behavioral inhibitory system may operate. (CONTACT PERSON: Dr. H. Tilson)

Neurobehavioral Test Methods Development -- Naturally occurring homecage behaviors will be used to assess the effects of known neurotoxicants such as trimethyl tin and acrylamide. The information derived from these studies may be useful in judging the applicability of such behavioral tests in the provisional assessment of chemicals for neurobehavioral toxicity. (CONTACT PERSON: Dr. H. Tilson)

NIOSH

FY 1984 ACCOMPLISHMENTS

Methods Development/Human -- A monograph was completed which describes recommended behavioral, neurological, and electrophysiological test methods and procedures to be used in assessing chemicals for neurotoxicity, particularly for developing countries where appropriate facilities and experience are at a minimum. The monograph developed out of the international World Health Organization (WHO)/NIOSH workshop "Neurotoxicity of Workplace Chemicals" held in Cincinnati in 1982. (CONTACT PERSON: Dr. B. Johnson)

Spray Paint Solvents -- Following acute exposures of human volunteers to toluene at recommended maximum occupational exposure concentrations, marginal effects on vigilance were found. The same subjects were also exposed to methyl ethyl ketone (MEK) singly at the maximum and in combination with toluene (both at half maximum) but no effects were noted. The results are being published in the International Archives of Occupational and Environmental Health. Similar findings following a more extensive neurobehavioral examination were included in the final contract report on chronic exposure of spray painters and printers to solvent mixtures. (CONTACT PERSON: Dr. R. Dick)

Alcohol/Aliphatic Hydrocarbon Solvents -- Offspring of pregnant rats exposed by inhalation to alcohols (methanol, ethanol, n-propanol, isopropanol, n-butanol) during gestation were examined for terata and behavioral changes (ethanol). Aliphatic hydrocarbons (n-hexane and MEK) were evaluated by one-time inhalation exposures of adult rats for four hours followed by neurobehavioral testing of reflex response and activity. (CONTACT PERSON: Dr. K. Anger)

Fumigants -- Behavioral deficits and symptoms of fumigant exposure were reported for fumigators using methyl bromide and sulfuryl fluoride. Extent of usage of carbon tetrachloride and carbon disulfide mixtures for grain fumigation and work practices associated with their use were studied at sites of grain storage. (CONTACT PERSON: Dr. K. Anger)

Neurotoxic Chemicals -- Four major reviews of behavioral toxicology were published or completed during the fiscal year. These provided a compilation of 850 neurotoxic chemicals, a critical review of worksite and human laboratory studies of neurotoxins, and a summary of animal behavioral teratology research. (CONTACT PERSON: Dr. K. Anger)

FY 1985 PROGRAM PLANS

Methods Development/Human -- Methods recommended by the WHO/NIOSH monograph will be introduced, along with other test methods and procedures, into the NIOSH worksite research program, and validation strategies will be developed and implemented to assess these methods. (CONTACT PERSON: Dr. K. Anger)

Spray Paint Solvents -- Human volunteers will be exposed for four hours under careful supervision, to methyl ethyl ketone (MEK) and acetone at half the NIOSH-recommended maximum concentrations for workplace exposures. Tests of vigilance, reaction time, memory, and body sway will be given before, during and after exposure to the chemicals. Blood and breath measures of body uptake will be taken concurrently. (CONTACT PERSON: Dr. R. Dick)

Alcohol Solvents -- Offspring of pregnant rats will be examined for terata following exposure to 2-butanol, 1-pentanol, 3-pentanol, and 1-hexanol and for behavioral changes following exposure to 1-propanol. Teratological endpoints will include skeletal and visceral variations, and behavioral tests will include measures of neuromuscular integrity, activity, sensory function, and learning ability. A methodological assessment of tests used in the NCTR inter-laboratory behavioral teratology project is planned as an outgrowth of this project through a workshop or conference with research scientists in this field. (CONTACT PERSON: Mr. K. Nelson)

Aliphatic Hydrocarbon Solvents -- Adult rats will be exposed for four hours to methyl amyl ketone and n-pentane, and then behavioral testing will be conducted using tests of activity and reflex startle response to an auditory stimulus. Tests will be conducted prior to the exposures and subsequent to them for one week. In conjunction with this project, the project officer will spend FY 1985 in Finland at the Finnish Institute for Occupational Health conducting a project of joint conception using startle reflex tests after aliphatic hydrocarbon exposures. Inter-laboratory comparisons will be undertaken in this joint research project. (CONTACT PERSON: Dr. J. Russo)

PULMONARY TOXICOLOGY

Contaminated air is a major source of human exposure to toxins both occupationally and environmentally. Because of the extensive surface area (80 M^2 in humans) of the pulmonary system brought into intimate contact with any inhaled airborne agent, the lung is often the target organ or the port of entry into the body. Epidemiologists are finding that pulmonary dysfunction is a principal predictor of mortality resulting from pulmonary and non-pulmonary disease. It is reasoned that pulmonary dysfunction leads to increased accumulation of toxicants and thereby acts as an initiator, promoter, or cofactor in the pathogenesis of numerous diseases. Hence, the evaluation of toxicants by inhalation exposure and the toxicologic evaluation of the structure and function of the lung are of critical importance.

NIOSH

One of the objectives of the NIOSH program in pulmonary toxicology is to compare pulmonary function with pathologic indices as predictors of respiratory disease in animal species -- tests of mechanical properties, gaseous distribution, static and dynamic lung volumes, distribution of inspired air, and more recently, ventilatory performance. A key issue in deciding to perform pulmonary function testing for detection of toxicity to the lung from inhaled substances is whether such tests provide any additional toxicologic information beyond that obtained from the pathologic evaluation of lung injury. Pulmonary function tests must be reproducible, sensitive, specific, and capable of large-scale utilization if they are to be used effectively in the diagnosis of early and subtle pulmonary lesions in experimental animal models that mimic chemically-induced pulmonary disease in humans.

FY 1984 ACCOMPLISHMENTS

Effects of Chemicals on the Pulmonary System -- The NTP interagency agreement with the Brookhaven National Laboratory continued. Final reports on three-and six-month exposures of Fischer-344 (F344) rats to Min-U-Sil (crystalline silica) were received. The data indicate that development of fibrotic lesions was more readily disclosed by morphologic evaluation and con-nective tissue analysis than by pulmonary function tests and radiographic methods. When rats were exposed for six months and then evaluated six months later, the fibrosis had developed to the extent that the high exposure group was distinguishable by physiologic and radiographic methods.

In another study under this agreement, F344 rats were exposed at 0.0, 0.3, 1.0, or 2.0 mg cadmium (Cd) (as $CdCl_2$ aerosol)/m^3, 6 hrs/day, 5 days/wk for 62 exposure days. All of the high dose rats died by the 45th exposure day. The lung lesions induced by the 0.3 and 1.0 mg Cd/m^3 exposures were used to compare measures of pulmonary mechanics and connective tissue composition to conventional morphological assessment. The predominant morphologic changes were found in the end airways. The observed hyperplasia and flattening of type II cells, inflammation, and proliferation of fibroblasts were dose dependent. Compositional alterations were generally in parallel with dose dependent increases in lung weights, except for hydroxyproline and elastin which were disproportionately high after exposure at 1.0 mg Cd/m^3. The restrictive functional lesion presented in the 0.3 mg Cd/m^3 group appeared to be primarily interstitial with reduced lung compliance and diffusion capacity and slightly augmented flow. After exposure to 1.0 mg Cd/m^3, the pronounced obstructive airflow observed was probably due to the enlarged airway-associated foci of fibrosis observed morphologically. In the case of cadmium induced lesions, the functional indices of parenchymal disorder correlated well with the relative concentrations of connective tissue and subjective scoring of the pathology.

In a final study under this NTP agreement, exposures of F344 rats and $B6C3F_1$ mice to cobalt (Co), tungsten carbide (WC), and a mixture of these in the approximate concentrations found in hard metal grinding and cutting tools were completed. Groups of rats were exposed to either filtered air, 1 mg Co/m^3, 15 mg WC/m^3, or the two dusts combined at these concentrations. The rats were studied both microscopically and physiologically. The mice were submitted for pathologic examination. Hematology end points were measured on both sexes of both species. Statistical assessment of these data is not complete at this time. (CONTACT PERSON: Dr. T. Lewis)

Fibrogenicity of Mineral Slags -- A study to evaluate the fibrotic potential of four coal slags is under way. The coal slags were administered by a single intratracheal instillation (40 mg in water) to Sprague-Dawley rats. Groups of rats were killed two days following instillation and at 3, 6 and 12 months later. Pulmonary function measurements were taken at these latter times. Pathology and data analyses are ongoing. (CONTACT PERSON: Dr. L. Stettler)

Vanadium -- Experimental procedures have been developed to evaluate the asthmagenic potential of vanadium pentoxide in nonhuman primates. Both immune and pharmacologic mechanisms are being studied as well as immediate and delayed responsiveness. Correlations among physiologic, immune, and pharmacologic indices will be made. Work identifying acute responses was incorporated into a manuscript for presentation to the American Physiological Society in August 1984. (CONTACT PERSON: Mr. W. Moorman)

Cotton Dust -- A new primate animal model for evaluating etiologic agents and chronic byssinotic effects was developed. Subchronic changes (aquired hyperreactivity or tolerance) in airway responsiveness to aerosolized aqueous cotton mill dust extracts were found that simulated the observed responses in cotton workers. Findings were reported at the 1984 Beltwide Cotton Production Research Conference. (CONTACT PERSON: Mr. W. Moorman)

Chronic Inhalation Studies with Diesel Exhaust and Coal Dust -- The experimental phase of this project was completed. It included a two-year inhalation study that evaluated the individual and combined effects of coal dust and diesel exhaust on pulmonary function, histopathology, serology and mutagenic effects in monkeys and rats and, in mice, infectivity studies, including causes of increased responses to influenza virus. All data were assembled, examined and analyzed and the results were reported at a tripartite meeting held at the NIOSH Cincinnati facilities on March 29, 1984. (CONTACT PERSON: Dr. T. Lewis)

FY 1985 PROGRAM PLANS

Pathology will be completed and the data from rats treated with coal slags will be analyzed. The asthmagenic potential of vanadium pentoxide will be studied further and a manuscript published. The asthmagenic potential of phthalic anhydride will also be investigated. Work previously initiated to determine the relative importance of proposed etiologic agents of byssinosis will be completed. (CONTACT PERSON: Dr. T. Lewis)

NIEHS

FY 1984 ACCOMPLISHMENTS AND

FY 1985 PROGRAM PLANS

Research in inhalation toxicology continuing through FY 1985 will include studies of the effects on the development of cleft palate in mice of time-varying concentration profiles and patterns of repetitive inhalation exposure to chloroform or toluene. Other studies are aimed at defining what property or properties of time-varying concentration profiles contribute to other expressions of the inhalation toxicity of chemicals, e.g., that of nitrogen dioxide and acrolein. Approximately 30% of the total chamber capacity will be devoted to direct support of the NTP testing program and the mineral fiber study program of the Intramural Research Program. Further development and refinement of the computer-assistance systems for the operation of the inhalation facility will continue through FY 1985 and will include, in part, studies of the systems using computer simulations that will be expected to improve their overall performance and utility. (CONTACT PERSON: Dr. E. W. Van Stee)

SAFETY EVALUATIONS OF ORTHO PHTHALIC ACID ESTERS AND RELATED COMPOUNDS

Ortho phthalate esters are widely used as plasticizers in synthetic materials, often comprising a substantial portion of the finished product. They can migrate to the environment and have been identified as universal contaminants of surface waters. Recent testing results from the National Toxicology Program indicate that the most commonly used plasticizer, di(2-ethylhexyl) phthalate (DEHP), is both hepatocarcinogenic and a male sterilant in rodent species.

The major objectives of this initiative are:

1. Perform structure-activity analyses to indicate whether additional class members should be tested for toxic potential.

2. Determine mechanisms for DEHP-induced carcinogenicity and reproductive failure to aid in defining human health risks.

These studies are utilizing a multidisciplinary approach to evaluating a class of chemicals, employing both short-term _in vitro_ and long-term intact animal testing, and mechanistically-oriented research.

NIEHS

FY 1984 PROGRAM ACCOMPLISHMENTS

Reproductive Toxicity -- The testicular toxicity of DEHP was found to be enhanced when animals were maintained on a low-zinc diet, although other biological effects of DEHP were unaffected by dietary zinc concentration. This suggests that gonadal deprivation of zinc is a likely mechanism of DEHP testicular toxicity. Preliminary studies have suggested that DEHP may impair the transfer of zinc into the testis.

Butyl benzyl phthalate (BBP) also caused atrophy of male rat gonadal tissue. The damage was accompanied by a severe depression of serum testosterone concentration along with increases in serum leutinizing and follicle stimulating hormones, suggesting normal functioning of the pituitary-hypothalmic axis. BBP also reduced bone marrow cellularity, suggesting a hematotoxic effect.

DEHP also was shown to be teratogenic in mice, but not in rats. Experiments monitoring the potential effects of this compound on neonatal growth and development were initiated. (CONTACT PERSON: Dr. W. Kluwe)

Toxicity Studies -- Two-year toxicology and carcinogenesis studies of diallyl phthalate in mice and rats were conducted, as were companion studies on the disposition and metabolism of the chemical in male rats and mice. Major species differences in toxic response were observed. (CONTACT PERSON: Dr. W. Kluwe)

Dermal Absorption -- The following phthalate esters were studied for their ability to be absorbed from rat skin after dilution in an ethanol vehicle:

dimethyl phthalate
diethyl phthalate
di-n-butylphthalate
diisobutylphthalate
di-n-hexylphthalate
di(2-ethylhexyl)phthalate
diisodecyl phthalate
butyl benzyl phthalate

In brief, phthalate ester absorption is reduced by increasing chain length and by chain branching. For example, there is considerable dermal absorption of diethyl phthalate, but minimal dermal absorption of diisodecyl phthalate. (CONTACT PERSON: Dr. W. Kluwe)

Chronic Toxicity, Disposition and Metabolism Studies of Diallyl Phthalate -- Major species differences were found in prechronic and chronic toxic response to diallyl phthalate (DAP). DAP was hepatotoxic in rats, ultimately causing cirrhosis, but not in mice. This difference appeared to be due to the relatively greater ability of mice to detoxify DAP metabolites such as allyl alcohol and acrolein. In chronic studies, DAP increased the occurrence of mononuclear cell leukemia in female rats, and equivocally increased the occurrence of lymphomas in male mice. Chronic diallyl phthalate administration also caused chronic gastric lesions (e.g., forestomach inflammation, hyperplasia) in mice. (CONTACT PERSON: Dr. W. Kluwe)

2-Ethylhexyl Compounds -- Four compounds containing a 2-ethylhexyl moiety --di(2-ethylhexyl)phthalate, di(2-ethylhexyl)adipate, tris(2-ethylhexyl)-phosphate, and 2-ethylhexyl acid sulfate -- were tested for chronic toxicity and carcinogenicity in rats and mice. All four compounds increased the occurrences of liver tumors in male and/or female mice, while only di(2-ethylhexyl)phthalate increased the occurrences of liver tumors in rats. These data suggest that 2-ethylhexylcontaining compounds may possess carcinogenic activity, especially for mouse liver. (CONTACT PERSON: Dr. W. Kluwe)

FY 1985 PROGRAM PLANS

Toxicity Studies -- Chronic diethyl phthalate toxicity studies by dermal exposure, mouse skin tumor initiation-promotion studies for dimethyl phthalate and diethyl phthalate, and a six-month subchronic toxicity study of butyl benzyl phthalate in male rats are being conducted. (CONTACT PERSON: Dr. W. Kluwe)

Mono(2-ethylhexyl)phthalate and 2-ethylhexanol, the products of di(2-ethylhexyl)phthalate hydrolysis, are being considered for toxicological evaluation. (CONTACT PERSON: Dr. R. Melnick)

Mechanism of Di(2-ethylhexyl)phthalate-Induced Hepatotoxicity -- In two-year toxicology and carcinogenesis studies conducted by the National Toxicology Program, di(2-ethylhexyl)phthalate (DEHP) was found to be hepatocarcinogenic in $B6C3F_1$ mice and F344 rats. Since DEHP also causes peroxisome proliferation, it has been suggested that the carcinogenicity of this chemical may be related to excessive peroxisomal production of H_2O_2. It is the objective of this project to examine the changes in H_2O_2 production from peroxisomal fatty acyl-CoA oxidation in livers of rats and mice treated with DEHP. Further assessment of an involvement of reactive intermediates of oxygen reduction in DEHP-induced hepatotoxicity will be made from measurements of: (a) activities of enzymes that eliminate toxic oxygen products (catalase, superoxide dismutase, glutathione peroxidase); (b) lipid peroxidation; and (c) superoxide anion radical production. Some groups have suggested that doses of DEHP which do not cause peroxisome proliferation would not pose a carcinogenic risk. Since the role of peroxisomes in DEHP-induced carcinogenicity is speculative, it is critical that this issue be resolved. This research project is part of NTP's effort to further characterize the toxicologic properties of DEHP. (CONTACT PERSON: Dr. R. Melnick)

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

This program area aims to develop a wide range of techniques for evaluating potential toxic effects of chemical exposure on the reproductive system and developing embryo as well as to improve current testing procedures for uncovering such effects. Several new testing procedures have been initiated with the goal of screening larger numbers of chemicals. With these under way, research efforts are beginning to focus more on better defining toxic endpoints, and developing information on cellular effects and alterations in underlying processes and how these are related to the ultimate outcome of reproductive or developmental toxicity.

FY 1984 ACCOMPLISHMENTS

The Coordinating Group, made up of representatives from NCTR, NIEHS, and NIOSH, met regularly to review ongoing programs, to assign new test chemicals to appropriate testing programs, and to plan further efforts for addressing program needs. In March 1984, the NTP Board of Scientific Counselors approved the formation of an Ad Hoc Advisory Review Panel made up of external experts. The Panel met in May for a program review.

NCTR ACCOMPLISHMENTS

Conventional Teratology Testing -- The testing of chemicals for teratogenicity has continued on contract in FY 1984. Thirteen studies on eight chemicals were completed, and an additional six studies (one postnatal) on four chemicals were under way (Table 22). One abstract on the teratologic evaluation of carbon disulfide was presented at the Society of Toxicology meeting in March 1984, and two abstracts on Bendectin® and ethylene glycol were presented at the Teratology Society meeting in June 1984. Selection of chemicals for conventional teratology testing in FY 1985 is under way and is being coordinated with the selection of chemicals for and results of the short-term *in vivo* reproductive toxicity assay and sperm morphology/vaginal cytology assay. (CONTACT PERSON: Dr. B. A. Schwetz, NIEHS).

Collaborative Behavioral Teratology Study -- Data verification from the five laboratories that evaluated standardized behavioral tests in a behavioral teratology protocol was completed in FY 1983. The final report on the intramural pilot studies was completed in FY 1984. Statistical analysis of the data is under way and includes a comparison of the results among the five laboratories. (CONTACT PERSON: Ms. J. Bulke-Sam)

In Vitro Teratology Test Development -- The list of agents for use in *in vitro* test validation was published in *Teratogenesis, Carcinogenesis, and Mutagenesis*, 3:461-480 (1983). Recommendations for additions and deletions will be considered. A repository for the agents was established by the NTP to provide a central source of chemicals for investigators interested in evaluating particular *in vitro* assays. Currently, 41 of the 46 chemical compounds selected are either in the repository or are on order, and are available to NTP in house projects. The repository is also intended to supply extramural laboratories, as supplies and resources permit.

The validation studies within the NTP agencies are proceeding. Currently, four systems are under study, spanning several levels of biological complexity, i.e., whole embryo culture, *Drosophila* and cell culture. NIEHS contracts comparing two cell systems were awarded at the end of FY 1983, protocol development took place during FY 1984, and testing will be initiated during FY

1985. The NCTR protocol on whole embryo culture has received final approval and testing on the first agent has been initiated. The NIOSH protocol for development of the *Drosophila* system was reviewed and approved by the NTP Board of Scientific Counselors, and will be carried out through an interagency agreement with Brookhaven National Laboratory. Finally, a draft concept proposal and cost estimate have been approved by the Ad Hoc Advisory Review Panel for the Program to support extramural validation studies of up to 10 *in vitro* systems. This concept proposal is now being revised for further review by the NTP Board. (CONTACT PERSON: Dr. J. Young).

NIEHS ACCOMPLISHMENTS

Fertility Assessment by Continuous Breeding -- Reports have been completed on 14 studies in this project (Table 23) and the laboratory segment of the second year of studies is being completed while the final set of 16 out of 48 studies are being started. Chemicals have been studied from the glycol ethers, polyglycol, phthalate ester, and methyl xanthine classes of chemicals as well as miscellaneous chemicals (Table 24). The study protocol has undergone minor modifications as the testing has progressed over the past two years and is currently designed to evaluate two generations exposed to the test chemical and concentrates on effects on fertility and offspring assessment. (CONTACT PERSON: Dr. J. Lamb)

Sperm Morphology and Vaginal Cytology Evaluation -- The sperm morphology and vaginal cytology evaluation has become a standard part of 90-day prechronic toxicity testing and new data have become available as the prechronic tests are completed. Over twenty chemicals have been evaluated using this system. The data are directly incorporated into the prechronic reports by the testing laboratories. (CONTACT PERSON: Dr. J. Lamb)

Male Reproductive Toxicology -- Methods have been optimized to obtain more useful information from the formalin-fixed testes of animals on prechronic or chronic test. The use of glycol methacrylate embedding of formalin-fixed tissues allows the possible re-evaluation of archival samples to improve data interpretation in male reproductive tract tissues. (CONTACT PERSON: Dr. R. Chapin)

Morphological and biochemical studies on the testicular toxicity of ethylene glycol monomethyl ether have been conducted and target cell types have been identified in rats treated with this glycol ether. Mating trials and morphological studies have also been conducted on dimethyl methyl phosphonate and methyl dopa in male rodents. (CONTACT PERSONS: Dr. R. Chapin and Dr. J. Dunnick)

Developmental Toxicity and Aromatic Halogenated Hydrocarbons -- Studies have been initiated on the interactions of different halogenated hydrocarbons with regard to their ability to alter normal development. Compounds are administered separately and in combination and the effects of combined chemical exposures are evaluated in the offspring. (CONTACT PERSONS: Dr. L. Birnbaum and Dr. J. Lamb)

Postnatal Toxicology -- Efforts are in progress to improve our ability to characterize the toxicity of chemicals to neonates relative to adults, and to explore the role of lactation in the induction of neonatal toxicity. The lactational process is evaluated as a source of exposure to chemicals secreted into milk and from the standpoint of nutritional support to the newborn. A pilot study with DDE was performed which, in addition to providing an opportunity to establish and validate various techniques, generated useful information about the capacity of this insecticide to influence various parameters of lactation, including milk production, milk composition (lactose, lipid, protein components), pup growth, and mammary gland integrity (at both the morphological and biochemical levels). Other investigations have been concerned with characterizing the secretion of the liver carcinogen, dimethylnitrosamine, into milk and measuring genetic toxicity in the neonate exposed via the milk. (CONTACT PERSONS: Dr. D. Kornbrust and Dr. B. Schwetz)

NIOSH ACCOMPLISHMENTS

Short-Term In Vivo Reproductive Toxicity Assay -- Two contracts awarded in FY 1982 were completed and results of testing 30 chemicals were received (Table 25). A new contract was developed and awarded for the resumption of this assay to develop preliminary reproductive toxicity data to assist in setting priorities for subsequent conventional testing. A total of 24 chemicals, listed in Table 26, are scheduled for testing under this contract. Continuing experience with this assay suggests that it is an appropriate method for developing data that are helpful when establishing testing priorities. (CONTACT PERSON: Dr. B. Hardin)

Reproductive and Developmental Toxicity of Glycol Ethers --Various studies of the reproductive and developmental toxicity of the glycol ethers were continued in FY 1984. Based on FY 1983 results in the short-term in vivo reproductive toxicity assay, diethylene glycol monomethyl ether was selected for teratogenesis testing by oral administration and the in-life phase of these studies was completed. A teratogenicity study by the dermal route comparing ethylene glycol monoethyl ether, ethylene glycol monoethyl ether acetate, ethylene glycol monobutyl ether, and diethylene glycol monoethyl ether was completed in which the first two glycol ethers were shown to be equivalent in teratogenic effects while no teratogenic effects were detected for the latter two glycol ethers. Proceedings of the September 19-21, 1983, NIOSH Symposium on Toxic Effects of Glycol Ethers were published in Environmental Health Perspectives, Volume 57, 1984. (CONTACT PERSON: Dr. B. Hardin)

Inhalation Reproductive Toxicity Studies -- An ongoing project is concerned with assessing the teratogenicity of industrial alcohols in rats. Thus far, methanol was found to be teratogenic at high inhalation exposure concentrations, ethanol was not teratogenic, and n- and iso-propanol were teratogenic at high concentrations. Evaluations of butanols are in progress, as is behavioral teratology of inhaled ethanol. Additional alcohols will be evaluated in the future. (CONTACT PERSON: Mr. K. Nelson)

An Interagency Agreement was established between the NTP and the Department of Energy Pacific Northwest Laboratories (DEPNL) under which inhalation reproductive toxicity studies will be conducted for selected NTP priority compounds. The agreement provides for a variety of tests, any one or a combination of which can be applied to each chemical: conventional teratology in rats, mice, or rabbits; behavioral teratology in rats; female fertility in rats or mice; male fertility in rats or mice; and mouse sperm head morphology.

Inhalation tests will be conducted at three exposure concentrations, and the specific test or combination of tests will be determined, based on the research gaps identified for each chemical. (CONTACT PERSONS: Dr. B. Schwetz, NIEHS and Dr. B. Hardin)

Development of a Short-Term Teratology Screening Method in Drosophila -- An Interagency Agreement was signed between NIEHS and the Department of Energy's Brookhaven National Laboratory (BNL) for validation studies to be conducted under the direction of NIOSH. As many as possible of the 47 chemicals included in the list of compounds for in vitro teratogenesis test validation (Smith et al., Teratogenesis, Carcinogenesis, and Mutagenesis 3:461-480, 1983) will be evaluated. (CONTACT PERSON: Mr. R. Schuler)

Development of Methods for Evaluation of Human Semen Quality as a Component of NIOSH Field Studies -- A laboratory was established and semen analysis techniques were developed. A concept review panel of outside experts reviewed these procedures. Characteristics of semen from workers exposed to ethylene dibromide (EDB) and ethylene glycol monoethyl ether were studied. Characteristics evaluated included: velocity and percent motile, determined from videomicrographic recordings of the fresh semen sample; sperm counts, per ml and per ejaculate; live sperm, by vital staining and by hypoosmotic stress; and sperm head morphology, using standard classifications of shape and microcomputer analysis of digitized sperm head perimeters. A contract was awarded to have sperm from the workers exposed to EDB evaluated for double fluorescence (YFF) bodies. Data from these studies are currently being analyzed. (CONTACT PERSON: Dr. S. Schrader)

Evaluation of N,N-Diethyl-m-Toluamide (MDET) for Reproductive Toxicity -- Male and female reproductive toxicities, including teratogenicity, of MDET, a widely used insect repellant, were evaluated. Studies in the Soviet Union suggested that offspring of exposed male and female rats have impaired postnatal survival. Although teratology is not complete, the current studies did not confirm those observations. An unexpected finding was partial hindlimb paralysis in treated adult rats of both sexes. (CONTACT PERSON: Dr. B. Hardin)

Cardiovascular Functional Teratology -- Methods are being developed for evaluating the functional status of the rat heart following in utero exposure to toxins. In the past year, electrocardiology (EKG) was employed to evaluate cardiac function in fetuses exposed to ethylene glycol monomethyl ether on days 7-13 of gestation. Abnormal EKGs were found. The data were presented at the 68th annual meeting, Federation of American Societies for Experimental Biology. (CONTACT PERSON: Dr. M. Toraason)

FY 1985 PROGRAM PLANS

NCTR PLANS

Conventional Teratology Testing -- Reports for current studies will be completed and testing will continue at the same capacity, i.e., 10-12 studies on 5-6 chemicals in two species per year. (CONTACT PERSON: Dr. B. A. Schwetz, NIEHS)

Collaborative Behavioral Teratology Study -- Statistical analyses of the data from the interlaboratory study will be completed during FY 1985. A workshop at which the data will be presented and future plans discussed is being planned for late FY 1985. (CONTACT PERSON: Ms. J. Bulke-Sam)

In Vitro Teratology Test Development -- The in-house studies will be continued and the systems evaluated as data become available. A primary effort will be in obtaining approval for the support of extramural studies and initiating the appropriate funding or contracting processes. (CONTACT PERSON: Dr. J. Young)

NIEHS PLANS

Fertility Assessment by Continuous Breeding -- The last set of chemicals in the evaluation of this testing system will be started this year and the data will serve both as information on the potential reproductive toxicity of specific chemicals and to judge the predictive capacity of the testing system compared to conventional testing systems. If appropriate, the system will then be used to test a limited number of chemicals per year and various strains and species will be evaluated to further optimize the testing system. (CONTACT PERSON: Dr. J. Lamb)

Sperm Morphology and Vaginal Cytology Evaluation -- These special evaluations will continue to be used as a part of the prechronic testing procedures and 15-month interim sacrifices in the chronic studies. Further improvements in the evaluation of sperm motility are being studied, such as videomicrography of live sperm samples for more precise sperm motility estimations. (CONTACT PERSON: Dr. J. Lamb)

Male Reproductive Toxicology -- Broader use of improved histologic techniques will be encouraged in the testing program. In vitro models of testicular toxicity will be initiated this year to compare various screening systems, endpoints and assay conditions. In-house studies are planned on acrylamide, ethylene glycol monomethyl ether and representative phthalate esters to compare specific in vivo testicular responses as potential screens for toxicity and to assist in the evaluation of the in vitro development efforts. (CONTACT PERSON: Dr. R. Chapin)

Developmental Toxicity and Aromatic Halogenated Hydrocarbons -- Studies are continuing on the effects of combinations of various halogenated hydrocarbons on development. These studies serve as models for studies on chemical interactions and toxicity. (CONTACT PERSONS: Dr. L. Birnbaum and Dr. J. Lamb)

Postnatal Toxicology -- Studies of the potential for DDE to affect lactation and alter neonatal development will be completed; the work on dimethylnitrosamine secretion in milk and the associated genetic toxicity in neonates exposed through the mother's milk will be finished. Studies will be initiated on other chemicals to relate neonatal toxicity to exposure through milk. (CONTACT PERSONS: Dr. D. Kornbrust and Dr. B. Schwetz)

Evaluation of Two In Vitro Teratogenesis Testing Systems -- The objective of the proposed research is to validate two in vitro cell culture systems for the detection of teratogens. Inhibition of ascites mouse ovarian tumor (MOT) cell attachment and human palatal mesenchyme (HEPM) cell growth will be measured in the presence of known teratogens and non-teratogens. The HEPM cell system has been reported to be complementary to the tumor cell attachment assay. Both assays will be run simultaneously.

Successful validation of these two systems will provide a screening system for detection of potential teratogens thereby improving the selection of chemicals for whole animal testing and the breadth of data on potential teratogens. (CONTACT PERSON: Dr. J. Lamb)

NIOSH PLANS

Short-Term In Vivo Reproductive Toxicity Assay -- The FY 1984 contract will be monitored, and previous results will continue to be used as a source of information as priorities are established for other tests. A compilation of data from all NTP-sponsored studies using this test will be completed. To the extent possible, data from similar EPA-sponsored studies will be included. This extensive data set will be evaluated to develop specific recommendations for necessary group sizes, to identify the most sensitive endpoints in this test, to establish the most appropriate methods of statistical analysis, and to recommend criteria by which test results can be systematically and consistently used to establish testing priorities. (CONTACT PERSON: Dr. B. Hardin)

Inhalation Reproductive Toxicity Studies -- In the ongoing inhalation teratology studies of industrial alcohols, additional alcohols will be tested for their ability to produce structural malformations, and potential behavioral teratogenic effects of propanols will be investigated in rats. Studies under the Interagency Agreement (NTP/DEPNL) began in FY 1984. For each chemical selected for testing, specific research gaps will be addressed and appropriate tests selected to develop a complete overview of the male and female reproductive toxicity. (CONTACT PERSONS: Dr. B. Schwetz and Dr. B. Hardin)

Development of a Short-Term Teratology Screening Method in Drosophila -- The Interagency Agreement (NIEHS/BNL) will proceed with initial training of BNL personnel and confirmation by them of NIOSH observations with chemicals previously tested in Drosophila. Thereafter, BNL will begin testing the known teratogenic and nonteratogenic chemicals in the list of compounds for in vitro teratology test development. (CONTACT PERSON: Mr. R. Schuler)

Development of Methods for Evaluation of Human Semen Quality as a Component of NIOSH Field Studies -- The contract for double fluorescence body (YFF) evaluation of sperm samples from ethylene dibromide-exposed workers will be completed. Additional field studies will be conducted if appropriate populations of workers exposed to potential reproductive health hazards are identified. (CONTACT PERSON: Dr. S. Schrader)

Cardiovascular Functional Teratology -- Methods will be developed for assessing the ability of the neonatal heart to respond to beta-adrenergic stimulation. (CONTACT PERSON: Dr. M. Toraason)

TABLE 22

DEVELOPMENTAL TOXICITY STUDIES COMPLETED OR IN PROGRESS IN FY 1984[a]

				Fetotoxicity			
Chemical	CAS No.	Species	Route[b]	Prenatal Death	Reduced Fetal Weight	Increased Malformations	Maternal Toxicity
Conventional Teratology Studies Completed in FY 1984							
Bendectin®	8064-77-5	Rat	Oral	+(800 mg/kg)	+(500 mg/kg)	+(800 mg/kg)	+(500 mg/kg)
Bisphenol A	80-05-7	Rat	Oral[c]				
		Mouse	Oral[c]				
Carbon disulfate	75-15-0	Rat	Oral	---	+(200 mg/kg)	---	+(100 mg/kg)
		Rabbit	Oral	+(25 mg/kg)	+(150 mg/kg)	+(150 mg/kg)	+(75 mg/kg)
Ethylene glycol	107-21-1	Rat	Oral	+(5000 mg/kg)	+(2500 mg/kg)	+(1250 mg/kg)	+(1250 mg/kg)
		Mouse	Oral	+(3000 mg/kg)	+(750 mg/kg)	+(750 mg/kg)	+(1500 mg/kg)
Hydrochlorothiazide	58-93-5	Rat	Oral[c]				
		Mouse	Oral[c]				
Sulfamethzine	57-68-1	Rabbit	Oral	+(1800 mg/kg)	---	---	+(1200 mg/kg)
Theophylline	58-55-9	Mouse	Oral (Drinking H_2O)[c]				
		Rat	Oral (Feed)[c]				
Triethylene glycol dimethyl ether	112-49-2	Mouse	Oral[c]				
Conventional Teratology Studies - Testing in Progress in FY 1984							
Diethylene glycol dimethyl ether	111-96-6	Mouse	Oral				
		Rabbit	Oral				
Ethylene glycol (postnatal study)	107-21-1	Rat	Oral	--	+(120 mg/kg)	--	--
Nitrofurazone	59-87-0	Mouse	Feed				
		Rabbit	Oral				
Triethylene glycol dimethyl ether	112-49-2	Rabbit	Oral				

[a] A+ indicates a positive effect; number in parentheses is the lowest dose at which the effect was detected.
[b] Dosing days 6-15 in rats and mice, days 6-19 in rabbits unless otherwise indicated.
[c] Final report not completed.

TABLE 23

STUDIES ON THE FERTILITY ASSESSMENT BY CONTINUOUS BREEDING PROTOCOL FOR WHICH A FINAL REPORT HAS BEEN COMPLETED

Chemical	Laboratory	Cas. No.	NTIS Number
Bisphenol A	RTI	80-05-7	-
Caffeine	EHRT	58-08-2	-
Caffeine	RTI	58-08-2	-
1,2-Dibromo-3-chloropropane	RTI	96-12-8	-
Di(2-ethylhexyl)phthalate	RTI	117-81-7	PB84181734
Diethylstilbestrol	EHRT	56-53-1	-
Diethylstilbestrol	RTI	56-53-1	PB84136746
Ethylene glycol	EHRT	107-21-1	-
Ethylene glycol monethyl ether	EHRT	110-80-5	-
Lead acetate	RTI	301-04-2	-
Methyl salicylate	EHRT	119-36-8	-
Methyl salicylate	RTI	119-36-8	-
Sulfamethazine	RTI	57-68-1	PB84136746
Theobromine	EHRT	83-67-0	-

EHRT = Environmental Health Research and Testing, Inc.

RTI = Research Triangle Institute

- = final report not yet listed in NTIS (National Technical Information Service)

TABLE 24

CHEMICALS UNDER STUDY IN THE FERTILITY ASSESSMENT BY CONTINUOUS BREEDING PROTOCOL*

Chemicals Tested at Two Laboratories	Cas No.
Caffeine	58-08-2
Diethylstilbestrol	56-53-1
Ethylene Glycol	107-21-1
Lead Acetate	301-04-2
Methyl Salicylate	119-36-8

Miscellaneous Chemicals	
9-Aminoacridine	90-45-9
2,2'-Bis(bromomethyl) 1,3-propanediol	3296-90-0
Bisphenol A	80-05-9
1,2-Dibromo-3-chloropropane	96-12-8
4-Hydroxyacetanilide	103-90-2
Propantheline Bromide	50-34-0
Sodium Saccharin	128-44-9
Sulfamethazine	57-68-1
Trichloroethylene**	99-01-6
Tricresyl Phosphate	1330-78-5

Phthalate Esters	
Di-n-butylphthalate	84-74-2
Di-n-ethyl phthalate	84-66-3
Di-2-ethylhexyl phthalate	117-81-7
Di-n-hexyl phthalate	84-75-3
Di-n-octylphthalate	117-84-0
Di-n-pentyl phthalate	131-18-0
Di-n-propylphthalate	131-16-8

Methyl Xanthines	Cas. No.
Caffeine	58-08-2
Theobromine	83-67-0
Theophylline	58-55-9

Glycol Ethers and Related Compounds	
Diethylene Glycol	111-46-6
Diethylene Glycol Monoethyl Ether	111-90-0
Ethanol	64-17-5
2-Ethoxy Acetic Acid	627-03-2
Ethylene Glycol	107-21-1
Ethylene Glycol Monobutyl Ether	111-76-2
Ethylene Glycol Monoethyl Ether	111-90-0
Ethylene Glycol Monoethyl Ether Acetate	111-15-9
Ethylene Glycol Monomethyl Ether	109-86-4
Ethylene Glycol Monophenyl Ether	122-99-6
2-Methoxy Acetic Acic	
Oxalic Acid	144-62-7
Propylene Glycol	57-55-6
Propylene Glycol Monomethyl Ether	
Triethylene Glycol	112-27-6
Triethylene Glycol Diacetate	
Triethylene Glycol Dimethyl Ether	112-49-2

* Selected chemicals will be tested more than once to evaluate inter-assay or inter-laboratory variations

** To be tested in rats and mice

TABLE 25

SHORT-TERM REPRODUCTIVE TOXICITY ASSAY RESULTS

	CAS. No.	PERCENT MATERNAL MORTALITY	VIABLE LITTERS	REDUCED SURVIVAL	NUMBER BORN		BODY WEIGHT	
					ALIVE	DEAD	BIRTH	GAIN
Allyl chloride	107-03-1	50	-	-	-	+	-	-
Cinnamaldehyde	104-55-2	0	-	-	-	-	-	-
Decalin	91-17-8	15	-	-	-	-	-	-
Di(n-butyl) phthalate	84-74-2	10	+*					
1,3-Dichloro-5,5-dimethylhydantion	118-52-5	18	-	-	-	-	-	-
Diethyl phthalate	84-66-2	4	-	-	-	-	-	-
Di(2-ethylhexyl) phthalate	117-81-7	0	+*					
Di(n-hexyl) phthalate	84-75-3	2	+*					
Di(iso-butyl) phthalate	84-69-5	54	+*					
Di(iso-decyl) phthalate	26761-40-0	0	-	-	-	-	-	-
Dimethyl methylphosphonate	756-79-6	2	-	-	-	-	-	+
Di(n-octyl) phthalate	117-84-0	0	-	-	+*	-	+*	-
Disulfiram	97-77-8	8	-	-	-	-	-	-
2-Ethoxy ethanethiol	17362-04-8	0	-	-	-	-	-	-
3-Ethoxy-1-propanol	111-35-3	26	-	-	+	+	-	-
2-Ethyl-1-hexanol	104-76-7	35	+	+	+	+	+	+
2-Ethylthio ethanethiol	26750-44-7	0	-	-	-	-	-	-
2-Ethylthio ethanol	110-77-0	0	-	-	-	-	-	-
N-Isopropyl-N'-phenyl-p-phenylenediamine	101-72-4	96	*					
2-Methoxyethyl acetate	106-74-1	0	+*					
2-Methoxyethyl acrylate	3121-61-7	30	+*					
Mono(2-ethylhexyl) phthalate	4376-20-9	12	+					
D-Phenylalanine	673-06-3	2	-	-	-	-	-	-
Probenecid	55-66-9	0	-	-	-	-	-	-
2-Propoxyethanol	2807-30-9	2	-	-	-	+	-	-
Tergitol NP-10	9016-45-9	0	-	-	-	-	-	-
Trioctanoin	538-23-8	6	-	-	-	-	-	-
Tris(2-chloroethyl)phosphate	115-96-8	0	-	-	-	-	-	-
Triton X-100	9002-93-1	2	-	-	-	-	-	-
Tween 60	9005-67-8	0	-	-	-	-	-	-

*NO VIABLE LITTERS PRODUCED

+ Statistically significant adverse treatment effect
- No statistically significant treatment effect
  Blank entries indicate statistical analysis was not feasible

TABLE 26

LIST OF CHEMICALS SELECTED FOR FY 1984 SHORT-TERM IN VIVO REPRODUCTIVE TOXICITY ASSAY

CHEMICAL	CAS No.
Acetaldehyde	75-07-0
Acetone	67-64-1
Benzaldehyde	100-52-7
Benzethonium Chloride	121-54-0
Benzyl Alcohol	100-51-6
Butyraldehyde	123-72-8
Cinnamaldehyde	104-55-2
Citral	5392-40-5
Crotonaldehyde	4170-30-3
Diethanolamine	111-42-2
Ethanolamine	141-43-5
3-Ethoxy-1-propanol	111-35-3
Formaldehyde	50-00-0
Furfural	98-01-1
Glutaraldehyde	111-30-8
Malonaldehyde	542-78-9
Probenecid	57-66-9
Propionaldehyde	123-38-6
13-Cis Retinoic Acid	4759-48-2
Trans Retinoic Acid	302-79-4
4,4'-Thiobis(6-t-butyl-m-cresol)	96-69-5
Triethanolamine	102-71-6
2,4,5-Trimethoxy-benzaldehyde	4460-86-0
Triorthocresyl Phosphate	78-30-8

COORDINATIVE MANAGEMENT ACTIVITIES

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200

CHEMICAL NOMINATION AND SELECTION

The chemical nomination and selection process remains integral to the effective long-term operation of the NTP with respect to both the testing of chemicals using current methodologies and the validation of new methodologies.

The following discussion briefly summarizes the current NTP chemical nomination and selection process. The process is shown schematically in Figure 4. (CONTACT PERSON: Dr. D. Canter)

NTP Chemical Nomination -- Member agencies of the National Toxicology Program and other sources (other Federal agencies, state agencies, the public, labor, industry) submit to the NTP nominations of chemicals for various types of toxicologic testing. The nominating sources are asked to submit the name of the chemical and the particular toxicologic tests desired; the rationale for the nomination; available background data on production, use, exposure, environmental occurrence; and extent of toxicologic characterization in a supporting summary document (Table 27). However, all nominations are considered regardless of the extent of the information submitted. Nominations should be addressed to: Chemical Nominations, National Toxicology Program, Room 2B-55, Building 31, National Institutes of Health, Bethesda, Maryland 20205.

Nominated chemicals are first reviewed by the NTP chemical selection coordinator to determine which chemicals have been tested, are already on test or scheduled for test, or have been previously considered and rejected for testing by the NTP or its predecessors. This preliminary examination of the nominations involves minimal searches of existing on-line data bases and reference books. Staff then examine the available literature, assess the relevant data, and prepare draft Executive Summaries for each chemical. (Draft Executive Summaries are not prepared for chemicals nominated solely for mutagenicity testing.) Included in each draft Executive Summary are: Chemical Identification, Surveillance Index (production, use, occurrence, analysis), Toxicological Effects, and Source of and Reason for Nomination. (CONTACT PERSON: Dr. D. Canter)

Evaluation of Nominated Chemicals -- The draft Executive Summaries are then sent to the Chemical Evaluation Committee (CEC), composed of representatives from the Consumer Product Safety Commission (CPSC), Environmental Protection Agency (EPA), Food and Drug Administration (FDA), Occupational Safety and Health Administration (OSHA), National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), National Institute for Occcupational Safety and Health (NIOSH), National Center for Toxicological Research (NCTR), and the National Toxicology Program (NTP). The CEC evaluates the draft Executive Summaries and recommends the types of testing to be performed. Primary and secondary reviewers are assigned to each chemical after consideration of the nature of exposure so that, to the extent possible, appropriate regulatory concerns will be addressed. Members are requested to search data bases unique to their agencies for further information on the nominated chemicals (and structurally related compounds) to improve the evaluation process.

At the CEC meeting the primary reviewer for each chemical summarizes the data on that chemical and makes recommendations for testing. The secondary reviewer presents additional information, where available, and also discusses the merits of testing the compound. Following a general discussion, the Committee votes on the recommended types of testing and assigns priorities for types of testing. The recommendations are based upon whether the chemical satisfies one or more of the eight NTP chemical selection principles (Table 28). Following the meeting, staff revises the Executive Summaries as needed and adds a section on the CEC testing recommendations.

Public Comment -- A Federal Register notice is published which lists the chemicals reviewed by the CEC and the recommended types of testing. Also, the notice solicits comments from interested parties including information on completed, ongoing, and planned testing in the private sector. Responses are requested within 30 days of the date of publication. The list of chemicals is also published in the NTP Technical Bulletin with a request for comments. These steps are taken to enable other individuals and groups to provide data useful to the NTP chemical evaluation process.

Peer Review -- The revised Executive Summaries and public comments on the nominated chemicals are then forwarded to the NTP Board of Scientific Counselors for review. The Board subsequently meets to evaluate these data and to make testing recommendations based on the available information.

Chemical Selection -- The Board's ratings and comments and pertinent public input are incorporated by staff into final Executive Summaries which are submitted to the NTP Executive Committee. The Committee decides whether to test, defer, or delete each of the nominated chemicals for the various types of testing. Executive Committee decisions are published in the NTP Technical Bulletin. The Committee also recommends priorities for testing and test methods development/validation to the NTP.

Following Executive Committee action, the NTP Steering Committee (see Organization section) refers the chemicals to one or more of the three agencies participating in the NTP: NIEHS, NIOSH, and NCTR. Each chemical is assigned to a chemical manager who assesses the data developed during the NTP chemical evaluation process and other information retrieved from detailed searches of the published literature. The manager also consults with industrial sources on such issues as mode of production, uses, worker exposure, planned or ongoing testing and availability of the chemical for testing. The manager then presents a proposal to the Toxicology Design Committee (TDC) either to perform appropriate toxicologic testing or to delete the chemical from consideration for testing. The TDC, which consists of scientists from NIEHS and NTP, assesses the proposal and either approves the protocols or returns the chemical to the Executive Committee with a recommendation not to pursue testing. The recommendation may be based upon technical difficulties in testing, budgetary reasons, or the existence of adequate outside testing.

All chemicals selected as a result of this process are then tested as time and resources permit.

Results of toxicological testing of selected chemicals are routinely reviewed to determine whether further types of testing are appropriate. Candidates for additional testing are then submitted to the NTP chemical nomination and selection process for evaluation and decision making.

FY 1984 ACCOMPLISHMENTS

NTP Chemical Nomination -- During FY 1984, 58 chemicals were nominated to the NTP for extensive toxicological testing. Table 29 lists the nominated chemicals, their CAS numbers, the source of the nominations and the recommended tests. The EPA also submitted seven aromatic amines and two aminophenols for testing in percutaneous absorption studies, utilizing a special experimental method.

The NIEHS staff submitted a proposal for *Salmonella* testing of 85 compounds. Thirty of these compounds represented the following four structural classes: chlorophenols, diarylamines, phenylenediamines and trisubstituted isocyanuric acid derivatives. The other 55 chemicals were found in the Love Canal dump site.

The EPA nominated 16 xerographic chemicals for testing in a number of genotoxicity systems, including the *Salmonella* assay and eukaryotic cell tests. Three methylquinoline compounds were nominated for genotoxicity testing in eukaryotic systems.

The Interagency Testing Committee nominated 1,2-dibromo-4(1,2,-dibromoethyl)cyclohexane for *in vitro* cytogenetics and mouse lymphoma assays because of its use as a flame retardant and the Committee's interest in its structure.

Evaluation of Nominated Chemicals -- During FY 1984, the Chemical Evaluation Committee (CEC) reviewed 25 chemicals and one group of substances that were previously nominated to the Program.

On November 8, 1983, the CEC evaluated 12 of these chemicals and the group of substances (black newsprint inks). Table 30 contains the chemicals, their CAS numbers, the testing recommendations with priority and remarks of the Committee.

On February 28, 1984, the CEC evaluated the other 13 chemicals nominated for toxicological testing. Table 31 lists the chemicals, their CAS numbers, the testing recommendations and CEC remarks.

Genotoxicity -- On November 8, 1983, the CEC approved a proposal submitted by the Interagency Testing Committee to test in the *Salmonella* assay chloro-thioformic acid, S-(n-propyl)chlorothioformate and S-(ethyl)chlorothioformate. The latter two compounds are pesticide intermediates. The CEC also approved a proposal submitted by a private individual to test seven compounds (four phenylureas and three nitroanilines), used as stabilizers-gelatinizers for nitrocellulose in smokeless powder/propellants, in the *Salmonella* assay. Both proposals were submitted in FY 1983.

On February 28, 1984, the CEC recommended the testing of 30 of the 85 chemicals proposed by the NIEHS staff for testing in the *Salmonella* assay. These 30 chemicals belong to the four structural classes mentioned above. The CEC deferred the remaining chemicals and recommended the development of a more comprehensive list of waste dump chemicals that would include the 55 Love Canal chemicals as well as chemicals found in other dump sites.

The CEC also recommended the testing of 1,2-dibromo-4-(1,2-dibromoethyl) cyclohexane in the *in vitro* cytogenetics and mouse lymphoma assays.

Public Comment -- To solicit public input into the chemical nomination and selection process, *Federal Register* notices were published on the chemicals evaluated for extensive toxicological testing at the November 8, 1983, and February 28, 1984, meetings. The notices appeared on January 9, 1984, and April 12, 1984, and requested the submission of relevant data and comments on the testing recommendations.

As a result of these notices, information on production and/or toxicology data were submitted by representatives of industry on the following compounds: C.I. Acid Yellow 151, C.I. Basic Red 18, C.I. Direct Red 80, C.I. Direct Yellow 4, C.I. Disperse Brown 1, Cinquasia Red and D C Yellow No. 11. The information received was summarized and made available to the Board of Scientific Counselors for its review of the nominated chemicals.

Peer Review -- On August 16, 1984, the Board of Scientific Counselors reviewed the 20 chemicals and a group of substances (black newsprint inks) evaluated by the CEC at its May 31, 1983, and November 8, 1983, meetings. The testing recommendations including priority for testing and additional remarks and/or caveats are summarized in Table 32. In addition, the Board reconsidered six nitropyrene compounds (1-nitropyrene, 1,3-dinitropyrene, 1,6-dinitropyrene, 1,8-dinitropyrene, 1,3,6-trinitropyrene, 1,3,6,8-tetranitropyrene) that were deferred on September 27, 1983. At that time, the Board requested that presentations on the current status of testing of this class of compounds be made at a future Board meeting to aid the Board in developing recommendations for these compounds. Accordingly, presentations were made to the Board by Dr. Jane Warren, The Health Effects Institute, and Dr. Steven Nesnow, EPA, on testing being performed by these groups. In addition, Ms. Alice Freund, representing the American Federation of State, County and Municipal Employees, AFL-CIO, which nominated these compounds, made a presentation on the rationale for their nomination. The Board recommended a complete battery of short-term tests for all the nitropyrenes, and carcinogenicity and reproductive effects testing for 1-nitropyrene and 1,8-dinitropyrene with a high priority.

Executive Committee -- The Committee selected 14 chemicals as Fiscal Year 1984 priority chemicals for indepth toxicologic evaluation. Thirteen of these chemicals were selected at the January 27, 1984, meeting, and one (gallium arsenide) at the August 31, 1984, meeting. The names and CAS numbers of these chemicals are listed in Table 33.

FY 1985 PROGRAM PLANS

Evaluation of Nominated Chemicals -- The Chemical Evaluation Committee (CEC) expects to review 40 to 45 compounds nominated for toxicology testing during FY 1985 and to select up to 100 compounds for mutagenicity testing in the *Salmonella* assay.

Public Comment -- *Federal Register* notices will be published to solicit input on the chemicals evaluated by the CEC during FY 1985.

Peer Review -- In FY 1985, the Board of Scientific Counselors will review 30 to 40 chemicals.

Chemical Selection -- It is anticipated that the Executive Committee will select 20 to 25 compounds as the FY 1985 priority chemicals for indepth toxicologic evaluation.

IDENTIFICATION OF TOXIC AND POTENTIALLY TOXIC CHEMICALS FOR CONSIDERATION BY THE NATIONAL TOXICOLOGY PROGRAM -- "TESTING NEEDS STUDY"

The National Academy of Sciences (NAS) was awarded a three-year contract in 1980 to address, according to the scope of work, the following issues: (1) the number of chemicals to which man may be exposed, either directly or through the environment; (2) the percentage of these chemicals that may have the potential for public health implications and thereby may need some type(s) of testing; and (3) the development of an approach for consideration by the NTP that will integrate, for the varying agency nominations at a point in time, the intensity of selected toxicity data elements, including absence of any data whatsoever, thereby estimating the relative potential for public health implications among those chemicals: a relative ordering system. The emphasis in this latter area was to be on process rather than the specific example for NTP consideration.

The final report for this NAS-NRC (National Research Council) contract was released in March 1984. The report "Toxicity Testing: Strategies to Determine Needs and Priorities," may be obtained from: National Academy Press, Publications Office, 2101 Constitution Avenue, N.W., Washington, D.C. 20418 for $22.50 per copy.

The report, based only on that data publicly available, concluded that the "select universe," the number of chemicals to which man may be exposed, either directly or through the environment, consisted of approximately 66,000 chemicals. This list is broken down into the following categories with the size of the category in parentheses after it: 1) Pesticides and inert ingredients of pesticide formulations (3,350); 2) cosmetic ingredients (3,410); 3) drugs and excipients used in drug formulations (1,815); 4) food additives (8,627); 5) chemicals in commerce: less than 1 million pounds/year (13,911); and 6) chemicals in commerce: production unknown or inaccessible (21,752). The report noted that pesticides and drugs have undergone the most testing. Least is known about the large number of chemicals in commerce -- substances listed in the Toxic Substances Control Act inventory that do not fall in the other regulated categories such as pesticides, cosmetics, drugs and food additives. Looking at these approximately 66,000 chemicals in a general sense, the report concluded that only a few have been subjected to extensive toxicity testing. In attempting to determine whether or not an assessment could be made for the potential for public health implications, the report concluded that information on the degree of exposure was even harder to find than data on health hazards.

With respect to setting priorities among any group of chemicals, the report proposed a four-stage process beginning with an initial screening by automated scanning of data banks and moving into greater reliance on expert judgment. (CONTACT PERSON: Dr. R. E. Shapiro, NIEHS)

FIGURE 4

NTP CHEMICAL NOMINATION AND SELECTION PROCESS

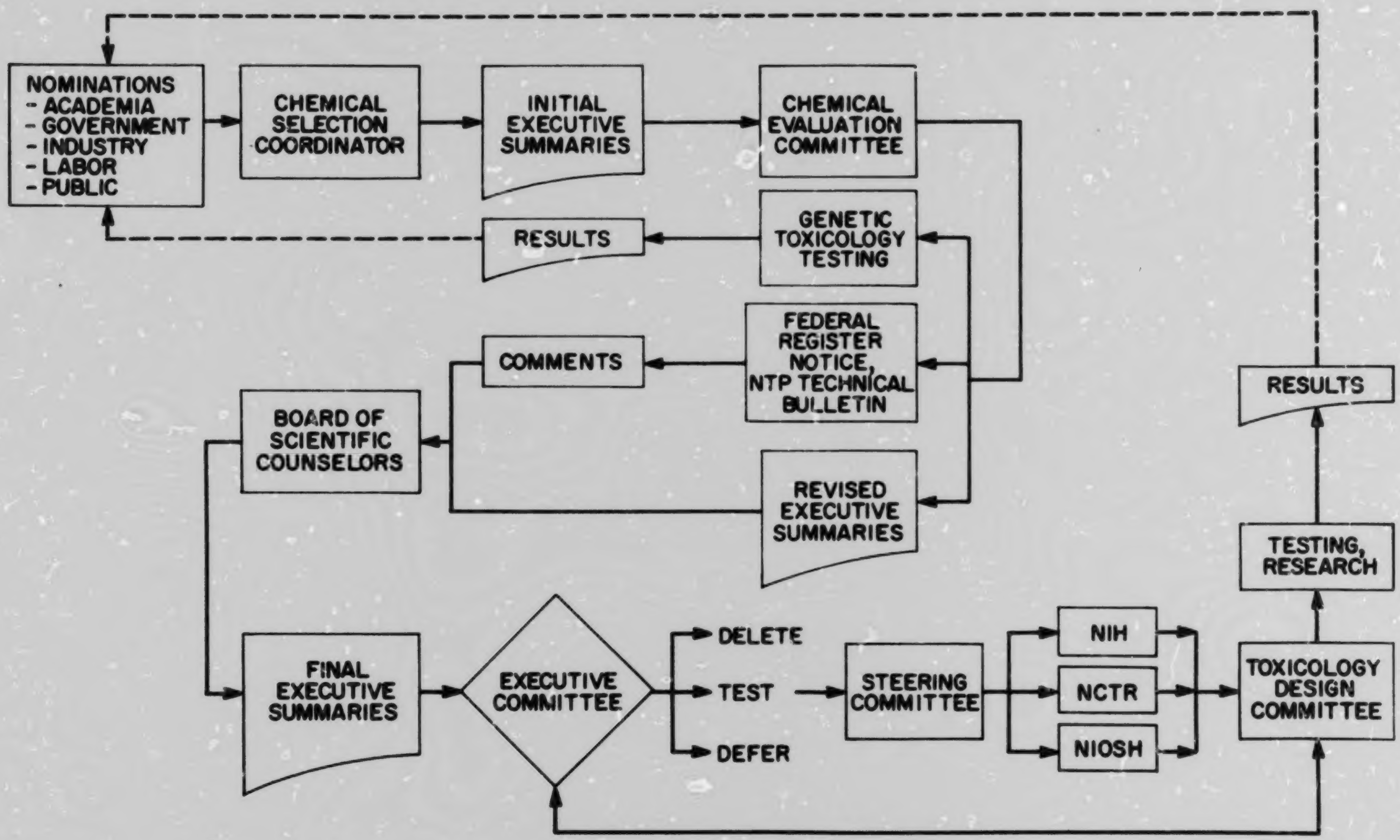
NOMINATIONS
- ACADEMIA
- GOVERNMENT
- INDUSTRY
- LABOR
- PUBLIC
CHEMICAL SELECTION COORDINATOR
INITIAL EXECUTIVE SUMMARIES
CHEMICAL EVALUATION COMMITTEE
RESULTS
GENETIC TOXICOLOGY TESTING
COMMENTS
FEDERAL REGISTER NOTICE, NTP TECHNICAL BULLETIN
BOARD OF SCIENTIFIC COUNSELORS
REVISED EXECUTIVE SUMMARIES
RESULTS
TESTING, RESEARCH
FINAL EXECUTIVE SUMMARIES
EXECUTIVE COMMITTEE
DELETE
TEST
DEFER
STEERING COMMITTEE
NIH
NCTR
NIOSH
TOXICOLOGY DESIGN COMMITTEE

TABLE 27

NTP CHEMICAL NOMINATION ELEMENTS

I. Chemical Identification

  a. Chemical Abstracts Service (CAS) preferred name
  b. Common or generic name and synonyms
  c. CAS Registry Number
  d. Chemical class and related compounds
  e. Physical and chemical properties

    i. Physical description
    ii. Structural and molecular formula and molecular weight
    iii. Melting and boiling points
    iv. Solubility
    v. Stability and reactivity
    vi. Other relevant information

  f. Commercial product(s) composition
  g. References

II. Production, Use, Occurrences, and Analysis

  a. Production

    i. Source and synthesis, year and pathway of first production
    ii. Current production and pathway

  b. Uses
  c. Occurrence in the Environment

    i. Naturally occurring
    ii. Air, water, and soil
    iii. Occupational

  d. Analysis
  e. References

III. Toxicology

  a. Human data, case reports, and epidemiological studies
  b. Experimental animal information
  c. *In vitro* and other short-term tests
  d. Other relevant information
  e. References

IV. Disposition and Structure-activity-relations

  a. Absorption, distribution, metabolism and excretion
  b. Structure-activity correlations and considerations
  c. References

TABLE 27 (continued)

V. Ongoing Toxicological and Environmental Studies in the Government, Industry, and Academia

VI. Rationale for Recommendation and Suggested Studies

TABLE 28

NTP CHEMICAL SELECTION PRINCIPLES

The NTP Executive Committee operates under the principle that industry will test chemicals for health and environmental effects as intended and mandated by the Congress under legislative authorities. Therefore, the NTP, acting under its chemical selection principles, will test:

1. Chemicals found in the environment that are not closely associated with commercial activities;

2. Desirable substitutes for existing chemicals, particularly therapeutic agents, that might not be developed or tested without Federal involvement;

3. Chemicals that should be tested to improve scientific understanding of structure-activity relationships and thereby assist in defining groups of chemicals that should be tested by industry;

4. Certain chemicals tested by industry, or by others, the additional testing of which by the Federal government is justified to verify the results;

5. Previously tested chemicals for which other testing is desirable to cross-compare testing methods;

6. "Old chemicals" with the potential for significant human exposure which are of social importance but which generate too little revenue to support an adequate testing program (some of these may be "grandfathered" under FDA laws);

7. Two or more chemicals together, when combined human exposure occurs (such testing probably cannot be required of industry if the products of different companies are involved); and

8. In special situations, as determined by the Executive Committee, marketed chemicals which have potential for large-scale and/or intense human exposure, even if it may be possible to require industry to perform the testing.

The selection of a chemical by the Executive Committee does not automatically commit the NTP to testing the chemical. The NTP is committed to ascertain the specific toxicologic and regulatory concerns; evaluate the adequacy of existing data or current efforts in government, academic, or private laboratories; and then propose and conduct specific tests that are needed. Occasionally new information is obtained that answers the questions posed in the nomination and selection process. Sometimes testing is not done because chemicals are withdrawn by the nominator, because others are or will be testing the chemical, or because the chemical is not available, or no longer produced.

TABLE 29

CHEMICALS NOMINATED IN FY 1984 FOR EXTENSIVE TOXICOLOGICAL TESTING

Chemical	CAS Number	Nomination Source	Recommended Testing
Aminophenols			
1. o-Aminophenol	95-55-6	EPA	-Dermal absorption -Chemical disposition
2. o-Aminophenol hydrochloride	51-19-4	EPA	-Dermal absorption -Chemical disposition
3. o-Aminophenol sulfate	67845-79-8	EPA	-Dermal absorption -Chemical Disposition
4. p-Aminophenol	123-30-8	EPA	-Dermal absorption -Chemical Disposition
5. p-Aminophenol hydrochloride	51-78-5	EPA	-Dermal absorption -Chemical disposition
6. p-Aminophenol sulfate	63084-98-0	EPA	-Dermal absorption -Chemical disposition
Benzodiazepines			
7. Chlorodiazepoxide	58-25-3	NIEHS	Toxicity and carcinogenicity
8. Clorazepate	20432-69-3	NIEHS	Toxicity and carcinogenicity
9. Diazepam	439-14-5	NIEHS	Toxicity and carcinogenicity
10. Oxazepam	604-75-1	NIEHS	Toxicity and carcinogenicity
Chloronitrobenzenes			
11. 2-Chloronitrobenzene	88-73-4	EPA	(Toxicological studies to determine effects on the hematopoietic and cardiovascular systems)
12. 4-Chloronitrobenzene	100-00-5	EPA	

TABLE 29 (Continued)

Chemical	CAS Number	Nomination Source	Recommended Testing
Glycol ethers and their acetates			
13. 2-Butoxyethanol	111-76-2	CPSC	-Subchronic studies -Carcinogenicity -Teratogenicity
		UAW International Union	-Mutagenicity -Carcinogenicity
14. 2-Butoxyethanol acetate	112-07-2	UAW International Union	-Mutagenicity -Carcinogenicity
15. 2-Ethoxyethanol	110-80-5	"	
16. 2-Ethoxyethanol acetate	111-15-9	"	
17. 2-Methoxyethanol	109-86-4		
18. 2-Methoxyethanol acetate	110-49-6		
Haloacetonitriles			
19. Bromochloroacetonitrile	83463-62-1	EPA	-Carcinogenicity
20. Dibromoacetonitrile	3252-43-5	EPA	-Carcinogenicity
21. Dichloroacetonitrile	3018-12-0	EPA	-Carcinogenicity
Methylquinolines			
22. 2-Methylquinoline	91-63-4	EPA	-Carcinogenicity
23. 2-Methylquinoline hydrochloride	62763-89-7	EPA	-Carcinogenicity
24. 4-Methylquinoline	491-35-0	EPA	-Carcinogenicity
25. 4-Methylquinoline hydrochloride	3009-43-0	EPA	-Carcinogenicity

TABLE 29 (Continued)

Chemical	CAS Number	Nomination Source	Recommended Testing
Nitrotoluene			
26. m-Nitrotoluene	99-08-1	EPA	-Toxicity and carcinogencity
27. o-Nitrotoluene	88-72-2	EPA	-Toxicity and carcinogenicity
Phosphines			
28. Dicyclohexylphosphine	829-84-5	EPA	Neurotoxicity using mammals other than rodents
29. Monocyclohexylphosphine	822-68-4	EPA	
29. Tri-n-butylphosphine	998-40-3	EPA	
31. Trioctylphosphine	4731-53-7	EPA	
Miscellaneous			
32. Arsenic trioxide	1327-53-3	NIEHS	-Carcinogenicity
33. Aspartame	22839-37-0	S. Walker	-Toxicity and Carcinogenicity
34. n-Butane	106-97-8	EPA	-Mutagenicity -Carcinogenicity
35. n-Butyl acrylate	141-32-2	EPA	-Mutagenicity -Carcinogenicity
36. Carbodox	6804-07-5	NIEHS	-Toxicity and Carcinogenicity
37. Catechol	120-80-9	NIEHS	-Toxicity and Carcinogenicity
38. Chlorowax 500C	63449-39-8	EPA	-Dermal absorption -Chemical disposition
39. C.I. Pigment Blue 15	147-14-8	EPA	-Mutagenicity -Toxicological evaluation
40. Cobalt naphthenate	61789-51-3	NCI	-Carcinogenicity

TABLE 29 (Continued)

Chemical	CAS Number	Nomination Source	Recommended Testing
Miscellaneous			
41. Di-(2-ethylhexyl)-sebacate (DEHS)	122-62-3	NIEHS	-Toxicological evaluation
42. 2,5-Diketopiperazine	106-57-0	S. Walker	-Toxicity and Carcinogenicity
43. Furan	110-00-9	NIEHS	-Inhalation carcinogenicity study
44. Furfuryl alcohol	98-00-0	NIEHS	-Toxicity and Carcinogenicity
45. 12-0-Hexadecanoyl-16-hydroxyphorbol-13-acetate (HHPA)	16561-29-8	Dr. C. Lawyer	-Carcinogenicity -Cocarcinogenicity
46. 4-(Hydoxyphenyl)-retinamide	65646-68-6	NCI	-Carcinogenicity
47. Isopentane	78-78-4	EPA	-Mutagenicity -Carcinogenicity
48. Kaempferol	520-18-3	NCI	-Pharmacokinetics
49. 5-Methoxypsoralen	484-20-8	FDA	-Oral photocarcinogenicity
50. Methylcyclopentadienyl manganese tricarbonyl	12108-13-3	EPA	-Multiple reproductive toxicity study
51. Methyl ethyl ketoxime	96-29-7	EPA	-Toxicity, subchronic studies, carcinogenicity
52. 2-Methylstyrene	98-83-9	EPA	-Toxicological evaluation
53. Monensin	17090-79-8	NIEHS	-Toxicity and carcinogenicity
54. Oxyphenbutazone	129-20-4	NIEHS	-Toxicity and carcinogenicity
55. α-Terpineol	98-55-5	NCI	-Carcinogenicity, including tumor initiation

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TABLE 29 (Continued)

Chemical	CAS Number	Nomination Source	Recommended Testing
Miscellaneous			
56. 1,3,5-Trichloro-1,3,5-triazine-2,4,6-(1H, 3H, 5H)-trione	108-77-0	NIEHS	-Toxicity and carcinogenicity
57. Tung oil	8001-20-5	Dr. C. Lawyer	-Carcinogenicity, -Cocarcinogenicity
58. Zeolites	1318-02-1	EPA	-*In vitro* studies using alveolar macrophages; *in vivo* studies using intrapleural injection, long-term inhalation chronic studies if intrapleural test results are positive.

TABLE 30

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED BY THE NTP CHEMICAL EVALUATION COMMITTEE ON NOVEMBER 8, 1983

	Chemical	CAS No.	Testing Recommendation (Priority)	Chemical Selection Principles	Rationale
1.	Arsine	7784-42-1	Comparative study of chemical disposition of arsine and arsenic trioxide (Low)	3	-Concern as an arsenic compound -Low level exposure to workers
2.	Black newsprint inks		-Skin painting carcinogenicity of two types of ink and of their petroleum pitch and petroleum oil vehicle components (High) -Chemical analyses of inks and their components to be performed prior to initiation of carcinogenicity studies (High)	4,5,8	-Generate animal data for comparison with epidemiological studies -Continuing worker exposure
3.	Cinquasia red	1047-16-1	Inhalational chemical disposition study (Moderate)	4	-Ascertain if chemical can be absorbed prior to considering it for other toxicological testing -Potential for worker exposure
4.	C.I. Acid Yellow 151	12715-61-6	No testing	-	-Low exposure -Chemical structure of low interest, particularly when compared to other azo dye nominations

TABLE 30 (Continued)

	Chemical	CAS No.	Testing Recommendation (Priority)	Rationale
5.	C.I. Basic Red 18	14097-03-1	Dermal chemical disposition study (Moderate)	-Positive in *Salmonella* assay -Interest in chemical structure
6.	C.I.Direct Red 80	2610-10-8	No testing	-Low exposure -Little interest in chemical structure
7.	C.I.Direct Yellow 4	3051-11-4	-Chemical disposition study -Carcinogenicity study if absorption demonstrated (Moderate)	Structure activity considerations
8.	C.I. Disperse Brown 1	23355-64-8	No testing	Not as interesting a candidate for testing as C.I. Basic Red 18
9.	D C Yellow No. 11	8003-22-3	-*Salmonella* assay -Dermal chemical disposition study -Oral carcinogenicity study (Moderate-Low)	-Regulatory interest as contaminant in D C Yellow 10, which is under review by FDA for permanent listing as color additive -Interest in quinoline structure
10.	Luminol	521-31-3	-*Salmonella* assay -Dermal chemical disposition study (Low)	-Lack of toxicity data -Exposure to small segment of population -Structure activity considerations

TABLE 30 (Continued)

	Chemical	CAS No.	Testing Recommendation (Priority)	Rationale
11.	Malathion	121-75-5	Defer pending receipt of reproductive studies from EPA	-Major agricultural commodity chemical -Under review by EPA for registration standard -Significant toxicological studies, including teratological and reproductive testing, underway or completed by industry
12.	Picloram	1918-02-1	Defer pending receipt of data from EPA	-Major agricultural commodity chemical -Registration standard to be published in early 1984 -Industry long-term feeding study underway in rats; other toxicology studies also undertaken
13.	Stannous fluoride	7783-47-3	No testing	-Stannous chloride negative in NTP carcinogenicity testing; sodium fluoride presently under test for carcinogenicity

TABLE 31

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED BY THE NTP CHEMICAL EVALUATION COMMITTEE ON FEBRUARY 28, 1984

Chemical	CAS No.	Testing Recommendation (Priority)	Chemical Selection Principles	Rationale/Comments
1. Chromium carbonyl	13007-92-6	-*In vitro* cytogenetics -Chemical disposition -Prechronic studies with emphasis on respiratory exposure (Moderate-High)	3	-Potential for human exposure -General toxicity of Cr(VI) compounds -Structural similarity to nickel carbonyl, a known carcinogen -NIOSH interested in respiratory study -Reconsider for carcinogenicity after completion of recommended studies
2. Ferric ammonium ferrocyanide	25869-00-5	-*In vitro* cytogenetics -Prechronic studies -Chemical disposition, including metabolism study (Low - Moderate)	3	Potential for human exposure
3. Ferrocene	102-54-5	-Carcinogenicity -Prechronic studies including sperm morphology vaginal cytology evaluation (SMVCE) (Moderate)	3, 4	-Interesting structure -Genotoxicity data indicate suspicion of toxicity -Consider reproductive toxicity study if SMVCE studies indicate toxicity
4. Octamethylcyclotetrasiloxane	656-67-2	No testing		-Lacks suspicion of toxicity -Reconsider if NCI mouse lymphoma test results are possible

TABLE 31 (Continued)

Chemical	CAS No.	Testing Recommendation (Priority)	Chemical Selection Principles	Rationale/Comments
5. Octamethyltrisiloxane	107-51-7	No testing		Lacks suspicion of toxicity
6. Triphenylantimony	603-36-1	No testing		Low production and exposure
7. Atrazine	1912-24-9	No testing		Adequate completed and ongoing toxicology studies
8. Ordram	2212-67-1	No testing		Adequate ongoing and completed toxicology studies by industry
9. Roundup	38641-94-0	No testing		Adequate industry testing
10. 2,3,4,6-Tetrachlorophenol	58-90-2	No testing		Adequate completed and current studies
11. p-Chloro-α,α,α-trifluorotoluene	98-56-6	Oral subchronic study in mice (Moderate-High)	1, 4, 6	Potential for exposure
12. Methyl isobutyl ketone	108-10-1	Defer		Deferred pending decision of EPA whether to require testing beyond subchronic study. CEC supports carcinogenicity testing of MIBK.
13. Gallium arsenide	1303-00-0	Subchronic study by intratracheal instillation, identifying target organ toxicity. (High)	3, 4	-Worker exposure -Increasing use trend -Data lacking on the combined toxic effect of gallium and arsenic. -Pending results of subchronic study, review for carcinogenicity study -Consider feasibility of doing a comparative toxicology study with another arsenic compound such as arsenic trioxide.

TABLE 32

TESTING RECOMMENDATIONS FOR CHEMICALS REVIEWED BY THE NTP BOARD OF SCIENTIFIC COUNSELORS ON AUGUST 16, 1984

Chemical (CAS No.)	Recommendation (Priority)	Remarks
1. Antimony potassium tartate (28300-74-5)	Subchronic study (Low)	-Past usage in U.S. -Current usage in other countries -Structural interest
2. Arsine (7784-42-1)	Comparative study of chemical disposition of arsine and arsenic trioxide (Low)	-Low occupational exposure
3. Black newsprint inks (No CAS Number)	Skin painting carcinogenicity studies on composite samples of each of the two types of ink, namely offset and letterpress inks. (High)	-Increased level of buccal and pharyangeal cancer among newsprint pressroom workers -Determine appropriate solvent control
4. 2-(2-Butoxyethoxy)-ethyl thiocyanate (112-56-1)	-*Salmonella* assay -Subchronic studies including sperm morphology and vaginal cytology evaluation -Short-term *in vivo* reproductive toxicity assay (Moderate)	-Potential for exposure -Structural interest -Evaluate for carcinogenicity testing upon completion of short-term studies
5. Chromic acid (13530-68-2)	Comparative chemical disposition study of chromic acid and sodium dichromate (Moderate)	-Occupational exposure -Increased incidence of pulmonary cancer in rats in sodium dichromate intratracheal instillation study
6. Cinquasia red (1047-16-1)	Inhalation chemical disposition studies (Moderate)	Potential for worker exposure

TABLE 32 (Continued)

Chemical (CAS No.)	Recommendation (Priority)	Remarks
7. C.I. Acid Yellow 151 (12715-61-6)	Deferred	Further information requested on rationale for nomination of the five dyes as representatives of azo and nitro dyes class
8. C.I. Basic Red 18 (14097-03-1)	Deferred	
9. C.I. Direct Red 80 (2610-10-8)	Deferred	
10. C.I. Direct Yellow 4 (3051-11-4)	Deferred	
11. C.I. Disperse Brown 1 (23355-64-8)	Deferred	
12. 2,3-Dichloropropylene (78-88-6)	-*Salmonella* assay -Mouse lymphoma, *in vitro* cytogenetics assays -Subchronic study -Carcinogenicity to be performed in tandem with another commercially important alkene (Moderate)	-Positive results in *Salmonella* assay -Structure activity considerations
13. Formic acid (64-18-6)	-Inhalational carcinogenicity study -Reproductive effects study (Moderate)	-High production and widespread exposure -Structural relationship to formaldehyde
14. Linolelaidic acid (506-21-8)	No testing	Refer to NCI for consideration of research on relationship between nutrition and cancer
15. Luminol (521-31-3)	-*Salmonella* assay (Moderate)	-Lack of toxicity data -Structural interest -Low exposure

TABLE 32 (Continued)

Chemical (CAS No.)	Recommendation (Priority)	Remarks
16. Methylene bis (thiocyanate) (6317-18-6)	-*Salmonella* assay -Chemical disposition study study -Subchronic study (Moderate)	-Structural interest -Potential for human exposure
17. Nitromethane (75-52-5)	-Carcinogenicity (Moderate)	-Interest in nitroalkanes
18. ß-Pinene (127-91-3)	Two-stage promotion study (Moderate)	-Structurally related compounds are tumor promoters -Potential for human exposure
19. Stannous fluoride (7783-47-3)	-Genotoxicity tests -Short-term *in vivo* reproductive toxicity assay (Moderate)	-Human exposure due to to use in dental
20. 1,2,4,5-Tetrachlorobenzene (95-94-3)	-*In vivo* cytogenetics -Acute neurotoxicity -Carcinogenicity including sperm morphology and vaginal cytology assays in prechronic portion of study -Short-term *in vivo* reproductive toxicity assay (High)	-Potential for exposure -Possible substitute for PCBs -Potential for bioaccumulation -Environmental occurrence
21. Thiophene (110-02-1)	-Subchonic study (Moderate) -Carcinogenicity (Low)	-Structural interest -Develop toxicological profile

TABLE 33

NTP FISCAL YEAR 1984 PRIORITY CHEMICALS FOR IN-DEPTH TOXICOLOGICAL EVALUATION

Chemical	CAS Number
1) Benzonitrile	100-47-0
2) Benzo(f)quinoline	85-02-9
3) Butyl benzyl phthalate	85-68-7
4) 1-Chloro-2-propanol	127-00-4
5) 2-Chloro-1-propanol	78-89-7
6) D and C Yellow No. 11	8003-22-3
7) 5,6-Dichloro-2-benzothiazolamine	24072-75-1
8) 2-Ethylhexanol	104-76-7
9) Gallium arsenide	1303-00-0
10) 6-Methoxy-2-benzothiazolamine	1747-60-0
11) 4-(6-Methyl-2-benzothiazolyl)benzenamine	92-36-4
12) Mono(2-ethylhexyl) phthalate	4376-20-9
13) m-Nitrobenzoyl chloride	121-90-4
14) p-Nitrobenzoyl chloride	122-04-3

CHEMICAL AND LABORATORY TEST MANAGEMENT

Chemical Managers -- Once a chemical has been selected for testing and referred to a particular program area, a NTP staff scientist -- designated the Chemical Manager -- is given the responsibility to ensure that the chemical receives a complete scientific evaluation. The Chemical Manager guides the chemical through each of the various testing phases and has the responsibility to: (1) know and understand the relevant scientific literature; (2) present a protocol designed to measure relevant endpoints to the Toxicology Design Committee; (3) participate in the selection of a contractor for performance; (4) monitor the experiment's progress and maintain current awareness of the literature for this and structurally related chemicals; (5) provide liaison with groups doing other studies on the chemical; (6) evaluate the data; (7) write the toxicology and carcinogenesis technical report; (8) present the technical report first to the internal peer review group and then to the Board of Scientific Counselors' Peer Review Panel; (9) prepare the final technical report and journal articles after Peer Review Panel approval; (10) respond to appropriate requests for information on that chemical; and (11) review the data audit on the chemical. The Chemical Manager also maintains a liaison with the nominators of the chemical, with the industry that manufactures or uses the chemical, and with appropriate governmental agencies that have a regulatory interest. (CONTACT PERSON: Dr. W. Kluwe)

As an adjunct, the Pathology Working Group, the Data Analysis Group, and the Quality Assurance-Good Laboratory Practices Section perform quality control functions. These groups ensure that: (1) an independent pathology laboratory examines slides from all target organs and tissues and 10 percent of all others; (2) studies are designed properly with regard to statistical requirements, and (3) the technical reports accurately reflect the data found.

Project Officers -- These are NTP staff scientists who are responsible for monitoring the overall operation of the contract laboratories performing toxicology and carcinogenesis studies for the Program and for ensuring that good laboratory practices are being followed. To establish that the tests are well conducted (scientifically, cost-efficient, and timely), these scientists initiate: (1) annual program reviews by peer groups of scientists; (2) quarterly site visits; (3) ad hoc visits by chemical managers and experts in various scientific disciplines as needed; (4) communication with the laboratory principal investigator and relevant NTP personnel; and (5) interaction with NTP contract specialists. These project officers/scientists are the Program's representatives in all dealings with the laboratories performing the toxicology studies. (CONTACT PERSON: Dr. W. Kluwe)

Quality Maintenance Procedures in the NTP -- Planning began during the first quarter of FY 1985 for a workshop to be held probably in September 1985 which will be concerned with all aspects of quality assurance. The workshop will be cosponsored by the NTP and the American Industrial Health Council (AIHC), and participation is expected by representatives of the NTP member agencies, other government agencies, industry, trade associations, NTP and non-NTP contract testing laboratories, academia, quality assurance associations, and health research and regulatory agencies from other countries. Preliminary goals of the workshop are: (1) to enhance awareness and understanding of Good Laboratory Practices (GLP), quality assurance and data audits; (2) to explore consistent standards for assuring and assessing quality of studies and study conduct; (3) to provide a forum for the exchange of ideas among government, industry, academia and other interested groups to discuss the techniques, methods and application of quality assurance; and (4) to strengthen a mutual commitment to quality assurance by government, industry, academia and other organizations involved in toxicology research and testing. (CONTACT PERSON: Dr. C. E. Whitmire, NIEHS)

DATA AUDITS

Data audits are integral to the high standards of quality assurance as conducted under the Toxicology Research and Testing Program (NIEHS/NTP). Whereas Good Laboratory Practices (GLP) regulations establish management responsibility in the testing laboratory for the proper conduct of non-clinical studies, comprehensive data audits are the only means of ensuring the integrity and quality of the study data. Because of the impact of NTP Technical Reports on public health issues relating to chemical toxicity and carcinogenicity, the data base upon which interpretive conclusions in Technical Reports are based must be validated. During FY 1983, data discrepancies detected in the methylene chloride studies conducted by Gulf South Research Institute led to a Program decision not to issue a Technical Report on these studies (Federal Register, Vol. 48, No. 151, p. 35508, August 4, 1983), or on any program study not yet printed unless a data audit has been completed.

Experimental data derived from toxicological/carcinogenesis studies are audited for completeness, consistency, and accuracy and to determine if experimental procedures are consistent with Good Laboratory Practices. Audit procedures deal mainly with these eight aspects.

(1) Administrative information -- Experimental protocol, statement of work, and correspondence.

(2) Pretest animal data -- Includes animal receipt (shipping tags), health at arrival, randomization to cages, randomization to groups, racks placed in rooms, quarantine observations, health when placed on study, and animal identification (individual and group).

(3) Chemistry information -- Includes chemical receipt (lots and when received/used), total amount used vs. amount received, methods of analysis, chemical analysis and reanalysis of test aliquots, referee samples, stability and homogeneity data, and corn oil analysis for peroxides.

(4) Dose preparation and administration -- Preparation and frequency of dosing, calculations for animals dosage, amount of chemical-vehicle mixture prepared and amount required to dose animals.

(5) Environmental conditions - (temperature, relative humidity, lighting, air changes) -- Equipment used, frequency of observation, mean conditions, fluctuations - range and duration.

(6) In-life observations -- Body weights, clinical signs and health, continuity through necropsy, mortality records and disposition. Individual Animal Data Records (IADRs).

(7) Pathology -- Review of necropsy observations for correlation with microscopic diagnoses, slide and paraffin block labelling and match, wet tissue bag labelling and correspondence with animal (wet tissue) identification, review of wet tissue for untrimmed lesions, and tissue accountability.

(8) Report -- Comparisons of established protocol, design and report methods and materials, collected data and report on clinical signs, chemistry, mortality, toxicology and pathology.

Since data audits were implemented in FY 1983, and through the end of FY FY 1984 (September 30, 1984), 43 two-year carcinogenesis studies conducted at 10 different testing laboratories have been audited (See Table 17 in Chemical Pathology Section). The laboratories where audits have been performed are: (1) Battelle Columbus; (2) Battelle Pacific Northwest; (3) Mason Research Institute; (4) Frederick Cancer Research Center; (5) Gulf South Research Institute; (6) Hazleton Laboratories America (Virginia); (7) Litton Bionetics, Inc.; (8) Papanicolaou Cancer Research Institute; (9) Southern Research Institute; and (10) Springborn Institute for Bioresearch, Inc. Additionally, there are other laboratories performing studies for the NTP (both ongoing and/or completed) for which audits have not yet been performed. These include: (1) Bioassay Systems Corporation; (2) Hazleton Laboratories America (Wisconsin); (3) International Research and Development Corporation; (4) Lovelace Inhalation Toxicology Research Institute; (5) Physiological Research Laboratories; and (6) SRI International.

Evaluation of audit findings for thirteen of these studies were finalized and draft technical reports evaluated by the Peer Review Panel in October 1983, March 1984, and July 1984 (Table 9). A summary of the audit findings was included in each Technical Report. Evaluation of findings from audits completed indicate that problems serious enough to compromise NTP's ability to interpret study results are restricted to the one testing laboratory. Guidelines for setting priorities in scheduling audits are:

(i) Studies on chemicals scheduled for peer review where pathology data have been evaluated and Technical Reports are being drafted.

(ii) Studies on chemicals for which Technical Reports have been written and approved by the NTP Board Technical Reports Review Subcommittee (Peer Review Panel), but not yet printed.

(iii) Studies on chemicals already printed and selected by the NTP Executive Committee's Subcommittee on Data Audits (some given priority equal to those in the previous category).

During the last quarter of FY 1984, in-life audits were begun at contract laboratories, approximately one per month. In-life audits usually will include one species and one sex and will be done on studies after 12 months on test, preferably at 15 months during or after the interim kill. Study priority will be based on identified or existing problems for specific chemicals or testing laboratory, and will be influenced by high early mortality, toxicity or neoplasia. (CONTACT PERSON: Dr. C. E. Whitmire, NIEHS)

FY 1985 PROGRAM PLANS

The NTP pathology archives were moved from Rockville, Maryland, to Research Triangle Park, North Carolina, during the first quarter of FY 1985. This will facilitate the audit process, as well as the overall pathology process. Under a new contract to be awarded in the third quarter of FY 1985, up to three new audit teams will continue retrospective audits at the archives. Each team should be capable of auditing from 18 to 30 studies per year. One team will be assigned to audit studies conducted at Gulf South Research Institute. As these new teams become adequately trained, the existing three audit teams will begin to focus more on in-life audits and GLP compliance at testing laboratories doing long-term studies and at contract facilities doing special studies (e.g., immunology, neurobehavioral studies, pharmacokinetics, reproductive effects, pathology support). (CONTACT PERSON: Dr. C. E. Whitmire)

CHEMISTRY RESOURCES

The chemistry program serves as a central resource for all testing and research activities of the NTP. Maintained to assure chemical quality and to minimize testing results variability due to external sources, the chemistry needs are facilitated via integrated contract mechanisms, an active in-house laboratory and cooperation and interaction with other NTP operations. The chemistry capabilities provide for procurement, chemical analysis, analytical methods development, purification and synthesis of test chemicals. In addition, a chemical repository resource has been established for the receipt, handling, long-term storage, shipment and preparation of chemical safety data handling sheets for approximately 3,000 chemicals.

Capabilities are provided for analysis of bulk chemicals, chemicals in test vehicles, methods development for quality assurance, including purity, stability (both bulk chemical and chemical/vehicle mixtures) and concentration determinations, chemical residue analysis of body tissues and fluids and special handling for residual and reprocured chemicals. In addition, capabilities exist for purification, derivation and synthesis of test chemicals. Trace level analyses of test chemicals for potential contaminants are available, when required, as well as provisions for percent level purity, stability and recovery analyses. Trace level chemical analysis may be necessary when known toxic impurities are suspected to be present in the test material. There may also be a requirement for trace analysis when toxicity tests of chemical mixtures or impure chemicals are positive and it is necessary to identify specific components that may be associated with the observed toxic effect.

FY 1984 ACCOMPLISHMENTS

The analytical services support contract established in FY 1980 continued to very actively support a large number of NTP programs. As in the past, the majority of the work was in support of the toxicology and carcinogenesis testing program. Fifty-four chemicals which were scheduled to begin some phase of study in FY 1984 were procured and/or analyzed prior to initiation of the study. In addition, 30 chemicals recently approved to start prechronic toxicity studies in FY 1985 have either been procured and analyzed or are currently being procured.

The chemistry performed at the contract testing laboratories is constantly monitored through review of their monthly reports and annual chemistry discipline site visits. During FY 1984, with the exception of procurement delays on several chemicals, there were no major chemistry related problems at any of the testing laboratories which would necessitate special visits.

Ten new chemicals were obtained for NTP teratology studies (Table 34). Analyses of these chemicals included complete bulk chemical purity and identity assays, methods development for bulk chemical stability, as well as chemical/vehicle mixing, stability and concentration assay methods. Information generated during the analysis of these chemicals was provided to the teratology program leader and the contract laboratory. Also, technical input in the area of chemistry and dose preparation was given on site visits to the teratology contract laboratory.

The chemistry resource continued support of the NIEHS reproductive toxicology's continuous breeding program whose contract initiative started in FY 1982. Seventeen chemicals were obtained for study in this program and distributed to the contract laboratories (Table 35). These chemicals were procured and analyzed in a similar manner to those obtained for the teratology program. In addition to the required bulk chemical purity and identity verification, the chemistry resource provided routine dose analysis for all chemicals on test in the program as well as interim bulk chemical reanalysis for purity.

The chemistry resource also continued support of the NTP's immunology program contract research by providing analytical chemistry services for the eight chemicals currently on study under this initiative (Table 36). Services provided were analogous to those provided for the continuous breeding program and included methods development and analysis of tissues for test chemical residues.

The chemistry resource continued support of the short-term in vivo rat liver model program contract initiative started in FY 1983. This support included dose level verification for phenobarbital, and butylated hydroxytoluene dosed feed pellets.

Continued support was provided to several NIEHS/NTP investigators in the area of chemical synthesis, tissues residue analysis and bulk chemical purity and dose mixture concentrations verification (Table 37). During FY 1984, tissue and body fluid residue analyses were performed on samples from chronic toxicity studies of dimethylbenzidine and dimethoxybenzidine, and a comparative toxicology study of nickel sulfate.

During FY 1984, the chemistry resource continued research into the possibility of microencapsulation as an alternative vehicle for administration of test chemical in the feed. Several chemicals including trichloroethylene and 2,6-xylidine were encapsulated with a gelatin/sorbitol matrix. Studies were done which included determining physical and chemical stability of the encapsulated material and feed mixes as well as an in-house study of the bioavailability of trichloroethylene after administration of microencapsulated material in feed. In addition, the newly established NIEHS/NTP chemistry resource laboratory initiated support of several in-house studies (Table 38).

The chemistry program also provides primary repository assistance to both the genetic toxicology and carcinogenesis testing programs. The two repositories which operate under similar standard operating procedures have undertaken numerous joint projects that demonstrate the integration of the two programs. During FY 1984, several hundred test and control chemicals were provided to investigators by the NTP Chemical Repository (see section on Chemical Repositories). (CONTACT PERSON: Dr. C. W. Jameson, NIEHS)

FY 1985 PROGRAM PLANS

The chemistry resource will continue to support the toxicology and carcinogenesis testing, teratology, reproductive toxicology, immunology, and the short-term in vivo rat liver tumor model programs by procuring and analyzing all new test chemicals.

Collaboration with in-house NIEHS/NTP investigators will be expanded through the operating in-house chemistry resource laboratory and the establishment of a local chemistry services support contract. Research activities to investigate the suitability of microencapsulation as an alternative vehicle for administration of test chemicals will continue to be actively pursued. (CONTACT PERSON: Dr. C. W. Jameson, NIEHS).

TABLE 34

CHEMICALS PROCURED AND ANALYZED FOR TERATOLOGY STUDIES IN FY 1984

CHEMICAL	CAS Number
Codeine	76-57-3
Diethylene glycol dimethyl ether	111-96-6
N,N-Diethyl-m-toluamide*	134-62-3
Ethylene glycol	107-21-1
Methyl DOPA	555-30-6
Nitrofurazone	59-87-0
Papaverine.HCL	61-25-6
Scopolamine hydrobromide	51-34-3
Theophylline	58-55-9
Triethylene glycol dimethyl ether	112-49-2

*Supplied to NIOSH

TABLE 35

CHEMICALS PROCURED AND ANALYZED FOR CONTINUOUS BREEDING PROGRAM IN FY 1984

CHEMICAL	CAS Number
9-Aminoacridine hydrochloride	134-50-9
2,2-Bis(bromomethyl)-1,3-propanediol	3296-90-0
Bisphenol A	80-05-7
Di(n-hexyl)phthalate	84-75-3
Ethanol	64-17-5
Ethylene glycol	107-21-1
Ethylene glycol monobutyl ether	111-76-2
Methoxyacetic acid	625-45-6
2-Methoxyethanol	109-86-4
Oxalic acid	144-62-7
Propantheline bromide	50-34-0
1,2-Propylene glycol	57-55-6
Propylene glycol monomethyl ether	1320-67-8
Tetraethylthiuram disulfide (Disulfiram)	97-77-8
Trichloroethylene	79-01-6
Tricresyl phosphate	1330-78-5
Triethylene glycol diacetate	111-21-7

TABLE 36

CHEMICALS PROCURED AND/OR ANALYZED FOR IMMUNOLOGY STUDIES IN FY 1984

CHEMICAL	CAS Number
1,3-Butadiene	106-99-0
Cadmium chloride	10108-64-2
Ethylene dibromide	106-93-4
1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin	19408-74-3
Nitrobenzene	98-95-3
Pentachlorophenol, Dowicide EC-7	87-86-5
Pentachlorophenol, Technical	87-86-5
1-Trans-delta-9-tetrahydrocannabinol	1972-08-3

TABLE 37

CHEMISTRY RESOURCE SUPPORT FOR TRTP IN-HOUSE STUDIES IN FY 1984

CHEMICAL (CAS No.)	Type of Study	Analysis Performed
Acrolein in nitrogen	Comparative toxicology	Procurement
Di(2-ethylhexyl)phthalate (117-81-7)	Comparative toxicology	Special Chemical/ Vehicle analysis Analyze animal tissues for Zn and Ca
Diethylstilbestrol (56-53-1)	Comparative toxicology	Dosage analysis
Diethylstilbestrol derivatives	Comparative toxicology	Synthesis
Dimethyl phthalate (131-11-3)	Comparative toxicology	Purity analysis
Methyl DOPA (555-30-6)	Comparative toxicology	Dosage Analysis
4-(N-Methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone	Chemical disposition	Synthesis-labelled and unlabelled
Nicotine precursors	Comparative toxicology	Synthesis of four compounds
Nitrogen dioxide in nitrogen	Comparative toxicology	Procurement
N-Nitrosodimethylamine (62-75-9)	Reproductive toxicology	Animal distribution study Stability study
Nitrosonornicotine (16543-55-8)	Chemical disposition	Synthesis-labelled and unlabelled
Oils (vegetable)	Genetic toxicology	Determine peroxide levels
Sodium cyclamate (139-05-9)	Comparative toxicology	Special Bulk/Special Chemical/Vehicle analysis
Sodium dodecyl sulfate (151-21-3)	Comparative toxicology	Limited purity analysis Dosage analysis

TABLE 38

NIEHS/NTP CHEMISTRY LABORATORY STUDIES

IN FY 1984

CHEMICAL (CAS No.)	Type of Study	Analysis Performed
DDT and metabolites (50-29-3)	Measuring levels of DDT and metabolites, notably DDE, in rats serum and milk samples.	Gas chromatography
Trichloroethylene (79-01-6)	Analysis of blood samples from cannulated rats given microencapsulated TCE and neat TCE in corn oil.	Gas chromatography
Vitamin D (1406-16-2)	Serum samples from rats exposed to normal light and yellow filtered light were analyzed for vitamins D_3 and D_2.	High Performance Liquid Chromatography
Toxicological interaction-7 chemical mixtures	Determination of maximum solubilities (up to 1%) of 7 mixtures of 4 compounds.	Spectrophotometric techniques

CHEMICAL REPOSITORIES

The NTP Chemical Repository program provides repository assistance to the toxicology and carcinogenesis testing, cellular and genetic toxicology, chemical pathology, and systemic toxicology programs. This includes: storage, location, and acquisition of approximately 1900 chemicals with a final capacity of 5,000 chemicals; and cataloging of Wisswesser Line Notations (WLNs), Chemical Abstract Service (CAS) numbers and numerous other pertinent pieces of information on chemical, physical and toxicological properties. This information is put into a custom-designed computer program which also generates randomized codes for various aliquots that are to be tested blind. Tracking and monitoring of repository functions are accomplished by a computerized data base management system which allows multi-tier access into a hierarchical system of data retrieval and file security. The repository, after searching through on-line computer data bases, edits and produces chemical specific handling documents both for day-to-day safe handling as well as for emergency situations, performs quality assurance (QA) tests for numerous NIEHS/NTP contract laboratories and ships these chemicals to national as well as international laboratories. Finally, upon completion of the animal testing studies, the repository receives and aliquots an archive sample of the chemical, then arranges for the environmentally safe disposal of surplus test chemicals. Thus, the chemical repository is involved in the entire toxicology testing cycle from beginning to end.

There are two separate repositories which have similar standard operating procedures; both divide the chemicals into three groups when quantities permit: a testing lot, an archive sample and a public allotment.

FY 1984 ACCOMPLISHMENTS

More than 800 aliquots were sent to investigators for toxicity testing in FY 1984, either as coded blind samples or as uncoded shipments (Table 39). Redesigned chemical specific safe handling documents and emergency procedure documents continue to provide clear and explicit handling procedures for these potentially toxic test compounds.

Flash point, density and vapor pressure determinations were initiated to meet shipping requirements and to assist testing personnel by supplying information on physical properties which are unavailable in the literature.

An apparatus for determining the permeation of glove materials by chemicals has been used to test glove permeability for a total of 100 NIEHS/NTP test chemicals with four different glove materials through FY 1984.

An addition to the Hazardous Materials Laboratory continues to enable storage of approximately 5,000, 500-gram samples at four different temperature levels (25°C, 5°C, -20°C and -70°C). A safe is also available for storage of controlled substances. A full Drug Enforcement Administration (DEA) license is in force.

A more refined computer software and hardware package for tracking and monitoring of chemicals has been implemented to meet the expanding needs of the NTP. (CONTACT PERSON: Dr. D. B. Walters)

FY 1985 PROGRAM PLANS

During FY 1985 the Chemical Repository program will continue to provide assistance to the NIEHS/NTP. Increased shipments are anticipated due to the expanded high priority testing battery of the Cellular and Genetic Toxicology program.

Combination of the repositories will proceed with a new repository contract at the beginning of FY 1985. Chemical analyses will be performed under a separate analytical chemistry services contract. (CONTACT PERSONS: Dr. D. B. Walters and Mr. A. T. Prokopetz)

TABLE 39

NTP CHEMICAL REPOSITORY HOLDINGS AND ACTIVITIES IN FY 1984

	Cellular and Genetic Toxicology Repository	Toxicology and Carcinogenesis Testing Repository
1. Control chemicals in inventory	6	-
2. Total number of unique chemicals	1400	550
3. Test chemicals shipped for *Salmonella* testing in FY 1984	200	-
4. Test chemicals shipped for *Drosophila* testing in FY 1984	80	-
5. Test chemicals shipped for cytogenetics testing in FY 1984	100	-
6. Test chemicals shipped for aneuploidy testing in FY 1984	30	-
7. Test chemicals shipped for cellular and genetic toxicology testing other than 3, 4, 5, 6	350	-
8. Aliquots shipped in FY 1984	800	30
9. Chemicals synthesized	0	-
10. Purity analyses performed	110	-
11. Quality Assurance samples analyzed	4	8
12. Chemicals selected for FY 1984 *Salmonella* testing	180	-
13. Chemicals selected for FY 1984 *Drosophila* testing	34	-
14. Chemicals selected for FY 1984 cytogenetics testing	50	-
15. Number of flash points determined	20	-
16. Number of chemicals tested in glove permeability study	60	-
17. Number of chemicals analyzed for solubility	500	-
18. Chemicals disposed	-	80

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LABORATORY ANIMAL RESOURCES

The laboratory animal resource provides genetically defined rodents of known microbial status for the NTP toxicology and carcinogenesis testing program. The rodent production program is designed to assure the timely supply of high quality disease free rats and mice for toxicologic and carcinogenic evaluation of chemicals. The production of quality animals is a cooperative effort between the rodent production facilities, the NTP and the contract toxicology testing laboratories.

One rodent production facility is currently under contract to provide specified numbers of F-344 rats and $B6C3F_1$ mice at weekly intervals for the NTP toxicology and carcinogenesis testing program. Rodents are also supplied by the Division of Cancer Treatment (DCT), NCI, at Frederick Cancer Research Facility (FCRF). Disease monitoring continues to be the priority for animal resources to maintain the quality of the animals supplied to NTP supported studies. One diagnostic laboratory under contract to DCT, NCI, is conducting disease monitoring of the rodent production facilities at monthly intervals. The sentinel animal program initiated in FY 1980 for prechronic and chronic toxicity and carcinogenicity studies continues to serve as the monitoring program for viral infections in each animal room at the toxicology testing contract laboratories. Genetic integrity of the production and test rodents is monitored by histocompatability (skin graft) or biochemical (isozyme electrophoresis) means under two contracts.

FY 1984 ACCOMPLISHMENTS

Rodent production is being modulated to provide adequate numbers of animals to all new study starts and to decrease any excess production. This procedure resulted in a decrease of rodent production to approximately 70% of the FY 1983 level, while maintaining and improving the quality of animals. One contract to start centralized rodent foundation colonies of C57BL/6N, C3H/HeN MTV-mice and F-344/N rats with pedigreed stock from the NIH repository was awarded in April 1984. This project will provide better control over the genetic integrity of the expansion stock for the future rodent production centers. Genetic monitoring was an important part of the rodent production program. In addition to the genetic monitoring conducted by the contractors for DCT, NCI, biochemical genetic monitoring of parent generations of inbred stock at all production centers supplying rodents to NTP studies is being conducted by an NTP contractor.

Information from the diagnostic assays of the sentinel animal program is being entered into computer files and periodic summary reports on frequency of positive viral determinations by year of termination of the study, by time on study, by chemical, by sex, and by laboratory and room number, for rats and mice are being prepared periodically to evaluate the animal care programs at the toxicology testing laboratories. Viral serology profiles as determined by the sentinel animal program are being included in the technical report of the chemical to assess the influence of viral infections on the effect of chemical, based on current knowledge and for future evaluation of virus-chemical interactions. Information from the sentinel animal serology file is being correlated with program wide incidences of lesions such as Sendai virus-pulmonary tumor association and mouse hepatitis virus-liver tumor association. Preliminary evaluations indicated no correlation between these virus infections and tumor incidence in these target organs of control mice.

Utero-ovarian infections and peritonitis of female mice in chronic studies are being monitored closely with continued efforts to isolate the causative agents, either primary or secondary. A research program under a contract is attempting to identify the bacterial isolates from these lesions by biochemical and serologic characters and to reproduce the lesions in the genital tract and peritoneal cavity of female mice using the isolates from the natural lesions of chronic studies.

FY 1985 PROGRAM PLANS

The animal resources will continue to produce disease-free, genetically defined rodents for the NTP testing programs. Additionally the following programs are planned:

1. Contractually starting two new rodent production facilities to replace the current production agreement and contracts expiring in September 1984.
2. Contractually initiating two diagnostic laboratories for disease monitoring of rodent foundation colonies, rodent production colonies and animals in the studies at the toxicology testing laboratories. These contracts will replace the agreements and contracts expiring in September 1984.
3. Developing programs and procedures to reduce or eliminate the viral infections of animals in future studies at the testing laboratories utilizing the reports on the frequency of viral infections by laboratory and by animal room of the sentinel animal data file.
4. Establishing acceptable limits for contaminants in the NIH 07 diet and evaluating the nutrient levels of NIH 07 diet with regard to their influence on the chronic toxicity and two-year carcinogenicity studies.

Each of these programs will enhance the overall goal of the animal resources programs to produce sufficient numbers of genetically defined disease-free rodents and to assist the toxicology testing laboratories in maintaining the test animals free of diseases. (CONTACT PERSON: Dr. G. N. Rao, NIEHS)

CHEMICAL HEALTH AND SAFETY

Toxicological characterization of environmental chemicals often involves short- or long-term exposure of humans and their environment to potentially hazardous materials. A chemical health and safety program must protect both the worker and the environment, conform to guidelines and regulations and help ensure the integrity of the study. Control of almost all health and safety concerns in this context center on an indepth knowledge of the chemical and physical properties of the test chemicals. In addition, successful administration of such a program necessitates interdisciplinary knowledge and cooperation with fields such as: industrial hygiene, engineering, toxicology, occupational medicine, information retrieval, biology, regulatory activities and program management. Input from chemical health and safety for NTP studies performed under contract begins with the initial experimental design to insure special requirements are met and to provide chemical-specific health and safety guidelines. Involvement continues through initial laboratory evaluation, follow-up site visits, program reviews, report monitoring, recommended changes in procedures, facilities design, etc., as well as response to emergency situations and concern with eventual waste disposal and record archiving. Included is maintenance of a program specific, state-of-the-art, chemical health and safety effort; chemical monitoring and industrial hygiene surveys; periodic review of training needs; and formulation of standards, guidelines and safety plans. Chemical health and safety coverage also includes the receipt, storage, shipment and handling of test chemicals by the Chemical Repository. In addition, the NTP Chemical Health and Safety Section advises and serves as an informational resource for in-house NIEHS/NTP efforts.

FY 1984 ACCOMPLISHMENTS

The areas of activity of the NTP Health and Safety program have been broadly characterized as including five types of effort: (1) tracking and monitoring; (2) chemical-specific health and safety packages; (3) quick response to technical requests; (4) communications and information; and (5) technical assessments and support.

During FY 1984, the reporting, recordkeeping, and archiving requirements of the NTP Health and Safety program have been significantly strengthened. In conjunction with this, the amount of maintenance activity to review, evaluate, and process information has markedly increased. These activities, which represent an on-going effort include: screening of the NIEHS/NTP Carcinogenesis and Toxicology Evaluation Branch (CTEB) laboratory monthly reports; annual summary analyses of CTEB contract laboratory reports; maintenance of up-to-date laboratory information notebooks; development of a health and safety package archive; tracking of laboratory safety plan updates; updating of archives; and preparation of quarterly schedule and status reports.

The preparation of chemical-specific health and safety packages is now being done for systemic toxicology test chemicals as well as for an increased number of CTEB chemicals. Also, health and safety data are developed for Superfund chemicals.

Unforeseen requests for quick-response assistance from the chemical health and safety program entailed: (1) the review of gas handling systems at two laboratories performing Salmonella assays; (2) evaluation of recirculation exhaust problems at an inhalation laboratory; (3) investigation of major ventilation air balance problems at a toxicity testing laboratory; and (4) conducting two contract pre-award site visits.

During the last two to three years, the NTP has developed minimum health and safety requirements for all types of toxicity testing laboratories, and strengthened the requirement that each laboratory have a safety plan. These activities have been based on an ongoing refinement of understanding of the special health and safety requirements of NTP contract laboratories. In addition, a needs/resources assessment conducted this year determined that there are virtually no training materials currently available which are suitable for the conditions, practices, and type of staff present at NTP laboratories. Training to raise health and safety awareness at laboratories is an important component of the overall health and safety program, and the growth of "right-to-know" laws has required employee training in selected jurisdictions. These factors, coupled with the absence of suitable training aids, have led the NTP Health and Safety Office to undertake development of a small number of slide/tape training packages.

Several projects have been undertaken to apply the principles of human factors engineering and design to improving health and safety in toxicity testing laboratory operations. For example, a study of dose preparation operations has been undertaken to characterize these operations and develop safety-related facilities design guidelines. In addition, work is in progress on development of a design for a necropsy and a tissue trimming station as well as a vented balance cover for weighing hazardous materials.

FY 1985 PROGRAM PLANS

Initial site visits have been made during the last two and a half years to all CTEB, cellular and genetic toxicology, systemic toxicology, and pathology contract laboratories active during FY 1983 and 1984. Having established a basic level of health and safety awareness at these laboratories, the site visit program has been reduced to a maintenance level of activity. Chemical Health and Safety resource staff will visit those cellular and genetic toxicology, systemic toxicology and pathology contract laboratories not previously visited (new contracts), along with selected other laboratories which lack strong safety programs or which have had significant facilities modifications. In addition, Chemical Health and Safety will continue to participate in the yearly program reviews conducted at all CTEB laboratories.

There is also a need to now provide as a resource to the NTP laboratories a compiled source of data on the technical background behind NTP's health and safety requirements. In addition, there is a need to supply information on alternative means of satisfying NTP's requirements (particularly for the smaller laboratory). To meet these requirements, an NTP Health and Safety handbook will be developed.

Work will continue on the development of training, design and evaluation projects already underway, as well as performance of tracking, monitoring, development and assessment duties. (CONTACT PERSON: Dr. D. B. Walters, NIEHS)

DATA MANAGEMENT AND ANALYSIS

NTP data management activities involve data processing and computer support for several of the NTP testing and test development programs. They include management of support contracts which provide services such as data collection, computer programming and report generation, and in-house development of management and administrative information systems.

The NTP also receives statistical research support from the Biometry and Risk Assessment Program of the NIEHS. These research efforts deal with various issues of experimental design, data analysis and interpretation of results from long- and short-term NTP studies. Specific research problems are discussed in detail below.

NIEHS

FY 1984 ACCOMPLISHMENTS

Data Processing Systems

CHEMTRACK -- Data base administration and software development continued on the CHEMTRACK management information system which provides the NTP with an interactive chemical tracking, report generation and ad hoc query system. Information on over 2000 chemicals exists in CHEMTRACK including chemical identification information, nomination/selection information and activities, milestone dates, test data and status information for the mutagenesis, carcinogenesis, immunology, chemical disposition and reproductive and developmental toxicology test programs and NTP publication information. The on-line component of CHEMTRACK resides on the Model 204 Data Base on the Parklawn Computer System. The major CHEMTRACK reports including the Management Status Reports and NTP Results Reports are generated by the in-house VAX 11/780 computer. (CONTACT PERSON: Mr. M. Rowley)

Development and operation of a Computerized Data Management System for the Cellular and Genetic Toxicology Branch -- During FY 1984 the Environmental Mutagenesis Information System (EMIS) contract with Bolt, Beranek and Newman (BBN), which had provided EMIS software development and operations support on the PROPHET computer since 1980, was terminated and the EMIS was moved to the in-house VAX 11/780. Laboratory data entry terminals developed by BBN continue to collect data on-line in the two *Salmonella* testing laboratories while forms are being used to collect *Drosophila* and cytogenetics data.

The EMIS provides data collection and editing, interactive data management and retrieval, report generation and statistical analyses for *Salmonella*, *Drosophila* (reciprocal translocations and sex linked recessive lethals), and cytogenetics (sister chromatid exchanges and chromosome aberrations) testing in the NIEHS Cellular and Genetic Toxicology (CGT) Branch programs.

Work has begun on developing data collection forms for transformation (SHE, SA7 and RLV) testing and on the transfer of the mouse lymphoma mutagenesis data from the IVIS system at NIH to the CGT data base on the VAX 11/780. (CONTACT PERSON: Mr. M. Rowley)

Carcinogenesis Bioassay Data System -- Management support was provided for the Carcinogenesis Bioassay Data System (CBDS), which for twelve years has supported the collection, computer storage and processing of data from chronic animal studies and the production of pathology tables, statistical analyses, weight gain, food consumption and survival curves for the NTP technical reports. Work continues on the transition from CBDS to the Toxicology Data Management System (TDMS). (CONTACT PERSON: Mr. M. Rowley)

Toxicology Data Management System (TDMS) -- The TDMS developed to collect data for chronic and pre-chronic studies, is now collecting in-life chronic and pre-chronic test data for all chemicals on test in ten NTP contract laboratories. The micropathology system is being utilized for all chronic tests in nine laboratories. There are data for approximately sixty chemicals on the TDMS data base. Pathology tables and summaries of in-life data are being produced on a routine basis. Detailed information on TDMS may be found in the NCTR entry of this section. (CONTACT PERSONS: Ms. N. Stegman and Mr. G. Nehls)

Systemic Toxicology Data Systems -- Systems support continued for the development of computer software for data collection via MINC and DEC Rainbow mini computers and RS/1 and SAS table production for immunology, reproductive and developmental toxicology and chemical disposition test data from the NIEHS Systemic Toxicology Branch. (CONTACT PERSON: Mr. M. Rowley)

Data Management Systems for Prechronic Studies -- Computerized data management systems supporting NTP prechronic studies and special reproduction and fertility studies were developed. In addition to facilitating storage and retrieval of data from individual studies, these systems provide access to a historical control data base for organ weight, hematology, clinical chemistry and reproductive and fertility parameters. (CONTACT PERSONS: Mr. S. Seilkop and Dr. J. Haseman)

Statistical Software Development for TDMS -- Statistical software for the Toxicology Data Management System (TDMS) was developed, providing facilities for the statistical analyses of pathology and survival data. The incidences of neoplastic and non-neoplastic lesions can be analyzed using methods which adjust for intercurrent mortality, and survival analyses include capabilities for generating high quality Kaplan-Meier plots. This software is completely interfaced to TDMS, and allows users to specify alternative statistical methods and select or pool data in generating their own statistical analyses. (CONTACT PERSONS: Mr. S. Seilkop and Dr. J. Haseman)

Statistical Studies

Exact conditional tests were developed for incorporating historical control data in testing for a trend in proportions. These procedures depend upon beta-binomial parameters, which are estimated from historical control data. (CONTACT PERSON: Dr. D. Hoel)

The effect of survival-adjusted analyses on the interpretation of increased tumor incidences was examined. Data from several recent NTP carcinogenicity studies were used to illustrate the misleading conclusions that can be drawn from the application of an inappropriate survival-adjusted analysis. For incidental tumors, logistic regression was proposed as a convenient method of adjusting for survival without the necessity of grouping the data into time intervals. This technique provides a framework for incorporating potentially confounding covariables, estimating the treatment effect, and testing a central assumption of the usual analysis. (CONTACT PERSON: Dr. G. Dinse)

A nonparametric estimator for the survival function was derived which accommodates censored survival times and uncertainty in the assignment of cause of death. Under certain assumptions the proposed estimator can be demonstrated to be consistent and asymptotically normally distributed. It was also shown that forcing the cause of death to be specified with certainty may result in substantial biases in some cases. In a related project dealing with diseases that can be classified as either definitely fatal, definitely incidental or unknown, an EM algorithm was developed that iteratively fractionates the animals with an unknown cause of death into the fatal and incidental categories. Prevalence and mortality functions were then estimated as if cause of death were known for all animals. The estimates at each iteration converge to the true maximum likelihood estimates. (CONTACT PERSONS: Dr. D. Hoel and Dr. G. Dinse)

The relationship between the Type I error of the Armitage linear trend test and the bioassay design was investigated. The results indicate that an improper design choice can cause the true Type I error to deviate significantly from the nominal value. These results were extended to include continuity corrected tests and survival adjusted procedures. (CONTACT PERSON: Dr. C. Portier)

The magnitude of false positive rates associated with laboratory animal testing for carcinogenicity continued to be investigated. These efforts are being expanded to include the examination of concurrent matched control groups to determine the presence or absence of extra-binomial variability. (CONTACT PERSON: Dr. J. Haseman)

Statistical considerations related to the use of estimated maximum tolerated doses (MTDs) in carcinogenicity testing were investigated. The loss of sensitivity associated with reducing the high dose from the MTD to 1/2 MTD was investigated by examining data from all NTP feeding studies carried out from 1979-1983. It was found that reducing the MTD to 1/2 MTD would have resulted in not detecting approximately 2/3 of the effects regarded as carcinogenic responses in these studies: (CONTACT PERSON: Dr. J. Haseman)

Statistical methods were developed for the analysis of in vitro cytogenetics data and applied to the first 22 compounds tested in Chinese hamster ovary cells by two NTP contact laboratories. Extensive analyses of split-flask and intra-flask control data led to the adoption of a Poisson sampling model for sister chromatid exchanges. Similarly, a binomial sampling model was adopted for the percentage of cells with chromosomal aberrations. In the case of each cytogenetic response, a trend test based on a regression of observed response on log-dose was employed. The concept of a weak positive control was introduced as a means of probing the sensitivity of a given laboratory with a particular assay protocol. (CONTACT PERSON: Dr. B. Margolin)

FY 1985 PROGRAM PLANS

Data Processing Systems -- Proposed work in FY 1985 will center around the continued transition of computer systems to the NIEHS in-house VAX computer and the transition of CBDS to TDMS. Additional development will proceed on CHEMTRACK, the administrative data base, and on systems developed for the NIEHS Cellular and Genetic Toxicology (CGTB) and Systemic Toxicology Branches. Support for the CGTB includes the continuation of development of cytogenetics and mouse lymphoma cell (L5178Y) data systems and the addition of new genetic toxicology test types as needed. (CONTACT PERSON: Mr. M. Rowley)

In FY 1985, the TDMS will be used for in-life data collection for chronic and pre-chronic tests. The micropathology system will be utilized for interim and terminal sacrifices as well as early deaths for all chemicals supported by the in-life system. Technical reports using tables generated by TDMS will be prepared. The ADABAS conversion will proceed and chemical managers will begin to make use of the query capability provided. Plans to rewrite the in-life portion of the system in order to give laboratories automated error correction capability and to improve the way clinical observations are collected will be formulated. New components will be added only after sucessful implementation of ADABAS. (CONTACT PERSONS: Ms. N. Stegman and Mr. G. Nehls)

Statistical Studies -- Further research will be carried out to modify test procedures incorporating historical control data to take into account the statistical variability in the estimation of beta-binomial parameters and to adjust for survival differences. (CONTACT PERSON: Dr. D. Hoel)

Efforts will be continued to identify and control sources of variability in historical control tumor rates and to establish a definitive historical control data base for NTP carcinogenicity studies. (CONTACT PERSON: Dr. J. Haseman)

Estimators of the incidence and prevalence functions for tumors which are only detectable at death will be investigated. The methods will be applied to the historical control animals to give baseline estimates of tumor onset in the NTP rodent species. (CONTACT PERSON: Dr. C. Portier)

A simulation study will be performed to investigate the performance of several survival-adjusted tests for a dose-response trend in the prevalence rates of tumors that are sometimes fatal and sometimes incidental. The power of the different tests will be compared when cause of death is assumed known for each animal individually, and the robustness of each test will be studied when all tumor occurrences are assumed to be incidental. (CONTACT PERSON: Dr. G. Dinse)

An effort will be made to produce independent empirical validation of a statistical analysis currently employed by NTP for the evaluation of Ames Salmonella test data. Additional work on the incorporation of historical control data in the analyses of cytogenetic data is envisioned. (CONTACT PERSON: Dr. B. Margolin)

NCTR

TOXICOLOGY DATA MANAGEMENT SYSTEMS

The Division of Toxicology Data Management Systems (TDMS) actively supports the NTP in several areas. Currently, this includes:

- Site Support (Contract Laboratories)
- Software Maintenance and Enhancement
- Software Development
- Central Computer Facilities
- Other projects as defined by the NTP.

FY 1984 ACCOMPLISHMENTS

Site Support -- The Experiment Information System (EIS) support was provided to the following contract laboratory facilities:

- Battelle Columbus Laboratories
- Bioassay Systems
- E.G. and G. Mason Research
- Hazleton Laboratories, America
- International Research and Development Corporation
- Lovelace Inhalation Toxicology Research Institute
- Microbiological Associates
- Southern Research Institute.

By the third quarter of 1984, EIS support was provided for 45 compounds in 79 chronic studies at the above listed laboratories. In addition, the following facilities received training and are being supported by the Post Experiment Information System (PEIS):

- Battelle Columbus Laboratories
- Battelle Northwest Laboratories
- E.G. and G. Mason Research
- Experimental Pathology Laboratories
- International Research and Development Corporation
- Midwest Research Institute/Pathology Associates, Inc.
- Southern Research Institute.

At these laboratories PEIS support was provided for 13 compounds in 24 chronic studies.

This support has included: initial site training, site liaison participation in study start-ups, distribution of user guides and standard operating procedures, updating and training on new releases of software and/or hardware, verification of data residing on production data bases, generation and distribution of mainframe reports, and on-site visits to participating laboratories.

In the spring of 1984 major efforts were directed toward upgrading Version 1 of the data collection terminals to incorporate most of the enhancements included in the Version 2 terminals. This process involved cycling the terminals from contract laboratories back to NCTR for hardware modification and recertification and then shipment back to the contract facilities. During this same time frame, certain of the Version 2 terminals were enhanced with additional memory to increase responsiveness of the pathology subsystems.

Software Maintenance and Enhancement -- Considerable effort has been expended in the area of mainframe report generation. Several of the EIS reports were modified to provide a greater degree of standardization among the reports. In addition, a number of specific modifications/enhancements identified by NTP were incorporated into these reports. Work was also begun on a report preprocessor to standardize the interface between the TDMS data bases and the various formatting programs. Minor modifications were also implemented on microprocessor generated reports.

The Histopathology Administrative System (HIAD) was upgraded to Version 1.1. Enhancements centered around improving the user interface, including such functions as report generation.

The Experiment Information System (EIS) was upgraded to Version 1.9 and was released to various contract laboratories. Some of the items Version 1.9 addressed were: the ability to add up to 255 entries in the Clinical Observation file; the addition of the date associated with the transfer of an animal to a hospital cage; an increase in the number of treatment groups from 16 to 32, modification of the touchpoint algorithm; and the ability to use the keyboard to acknowledge entry of the correct manual time.

Numerous requests for enhancements to the PEIS have been made by the NTP. These requests were segregated by priority into a Version 2.3 and a Version 3.0. Version 2.3 included items that would enhance the quality assurance and audit processes, such as an inventory sheet, an animal disposition summary, and an experiment information summary. Version 3.0 encompasses additional functions and items to improve response time. These include: entry of cause(s) of death; the identification of sites within a metastatic tumor primary site; the entry of the GLP tracking date; identification of multiple sets of protocol-required tissues per treatment group; and entry of longer notes. Data entry time saving items include: more extensive memory mapping made possible by the addition of memory boards; a mechanism to define a set of frequently used observations and then choose those observations with limited screen paging; and standardization of the control points across screens. Version 3.0 is scheduled for release during FY 1985.

Software Development -- During FY 1984 work was begun on the analysis of a Version 2.0 of TDMS. This effort initially focused on the implementation of the

Software AG DBMS package, ADABAS, and the conversion of the existing TDMS data bases to this commercial software package. During this time the services of a group of independent data base consultants were obtained to assist in the development of the conversion and implementation plans. While initially emphasizing the data base portions of TDMS, this development activity will eventually involve an indepth evaluation of all data collection and reporting software.

Central Computer Support -- We are currently supporting 29 NCTR experiments, 165 NTP experiments, and 11 experiments for other agencies. There are a total of 21,069 cage records on the Experiment Information System (EIS) data base and 13,286 animal records on the Post Experiment Information System (PEIS) data base. Data base updates process approximately 10,000 transactions nightly.

FY 1985 PROGRAM PLANS

Plans for the TDMS for FY 1985 include a continued expansion in both the number of laboratory sites and the number of studies being supported by TDMS. All new chronic study starts on existing contracts will be fully supported by TDMS as well as all chronic studies from newly awarded testing contracts. In accordance with NTP direction, TDMS will be implemented for support of selected 90-day prechronic studies. For specified ongoing chronic studies selected by NTP, support will be given for collection and management of the pathology data generated by those studies.

The major software activities to be addressed in FY 1985 will include:

- Continued development of Version 2.0 of TDMS
- Development of micropathology Version 3.0
- Evaluation of new support requirements (e.g., gross pathology, clinical pathology, analytical chemistry)
- Continued refinements of existing systems
- Expansion of data reporting capabilities.

(CONTACT PERSON: Mr. G. Green).

INFORMATION GENERATION AND DISSEMINATION

Communication of scientific information about toxic and potentially toxic chemicals remains a critical aspect for program success and is one of the Program's four specific goals. The National Toxicology Program determines the toxicology of selected chemicals and must assure that results have scientific validity and regulatory usefulness. The end product is information -- scientific information for deciding social issues relative to public health and the environment. This has two important aspects. First, information must be disseminated to other scientists so that peer review and feedback assure scientific quality; second, since the scientific product helps society evaluate identified toxicologic risks, information must be disseminated to not only the regulators responsible for protecting against potentially hazardous risks, but also to those exposed to the risks.

The value of scientific information depends in part upon the quality and timeliness of information the Program receives from many sources: Federal, state and local governments; trade associations; industry; labor; academia; professional societies; public interest groups; the press; individuals; other countries; and other interested parties. This includes: nominations of chemicals to be tested; critiques and questions about scientific procedures, policies, priorities, and resource allocations; suggestions for program improvement; and most importantly, information about planned, ongoing, and recently completed studies on chemicals being considered for testing or being tested by the NTP.

Scientific Coordination and Information Dissemination -- The NTP Board of Scientific Counselors convenes three times a year in public forum, as does the Board's Peer Review Panel whose members evaluate draft technical reports on toxicology and carcinogenesis studies.

To remain aware of scientific procedures and results produced by other laboratories, the second part of the Annual Plan, the Review of Current DHHS, DOE and EPA Research Related to Toxicology, contributes toward this goal. This document provides overviews of research programs as well as information on chemical testing and test methods development activities in the various agencies. Work in progress and communication links among investigators worldwide are integrated with many national and international organizations and are being pursued with others.

Fundamental to current awareness is the ready availability of comprehensive searches and reviews of the scientific and technical literature on a given compound in advance of decisions about testing priorities and experimental test designs. This is of special importance for the toxicology and carcinogenesis testing program, where the testing process for each chemical represents a major commitment of time, labor, materials and funds for up to a five-year period. The online services from the National Library of Medicine (NLM) are particularly valuable: CHEMLINE, TOXLINE, RPROJ (Research Projects), MEDLINE, CANCERLINE, TOXICOLOGY DATA BANK, RTECS (Registry of Toxic Effects of Chemical Substances), and others. These and other sources are used to prepare dossiers on chemicals nominated for test and to provide information for the design of test protocols. Also, new information services will need to be located or developed for toxicology specialties not yet covered adequately in existing systems. (CONTACT PERSONS: Dr. P. Craig, NLM, and Ms. F. Jordan, NIEHS)

The Environmental Mutagen Information Center (EMIC), supported by the NTP, collects, organizes, and disseminates, primarily, published information on chemicals tested for mutagenicity. Located since its inception in 1969 at the Oak Ridge National Laboratory (ORNL), the EMIC computerized data file contained (as of September 30, 1984) 52,146 records on 17,193 unique chemicals, 43,721 of which are available on-line from TOXLINE (at the NLM) and 50,995 from RECON (at the ORNL). Each record contains bibliographic information, assay systems, and keywords defining agents tested and organisms studied. (CONTACT PERSONS: Mr. S. Stasiewicz, NIEHS, and Mr. J. S. Wassom, ORNL)

The Environmental Teratology Information Center (ETIC) was established in 1975. Through an Interagency Agreement with the Department of Energy (DOE), the services and facilities of the ORNL were obtained to maintain this computerized information system. The ETIC file contains references to published literature about environmental agents tested for or known to induce teratogenic effects. As of September 30, 1984, a total of 34,599 references had been collected with 31,601 available online from TOXLINE and 31,799 available online at RECON. These references contain information about 6,400 unique chemical agents identified with the Chemical Abstract Service Registry (CAS) numbers and 850 agents without CAS numbers. Each record is indexed with bibliographic information, language, publication type, systems studied or systems affected by test agent, keywords defining agents tested, CAS number and organisms studied. (CONTACT PERSONS: Mrs. F. E. Jordan, NIEHS, and Mr. J. S. Wassom, ORNL)

Technical Report Preparation and Dissemination -- Chemical managers (toxicologists) are provided with the relevant information to design experiments and to oversee the progress of a compound from selection through toxicology and carcinogenesis testing to final report preparation and distribution. Preparation of the technical report begins with selection of a chemical for testing and the appointment of a chemical manager. Each manager is responsible for recommending and designing the appropriate experiments, for records management and experiments monitoring throughout the test/research period, for preparation of the draft toxicology and carcinogenesis technical reports, and for presenting/defending these reports before the Peer Review Panel. While experiments are in progress, the chemical manager interacts with other Government agencies and serves as resource person for scientific inquiries concerning the chemical and its possible adverse effects. Lists of chemicals nominated and scheduled for testing, those on test, and those completed are published in the *Federal Register*, the NTP *Annual Plan*, and the *NTP Technical Bulletin* as well as being distributed to a variety of newsletters and scientific magazines.

Data from the toxicologic characterization studies and the chronic exposure experiments are collected into comprehensive and evaluative technical reports. After the draft receives staff approval, copies are sent for external peer review to the NTP Board of Scientific Counselors' Peer Review Panel. At this stage draft reports are made available to any individual or organization seeking or requesting copies as long as supplies last. The Peer Review Panel, comprised of non-government scientists, then reviews critically these draft reports and gives their opinions and findings in sessions open to the public. (Routinely, comments and questions are requested from the individuals or groups attending these open meetings.) After the draft reports are considered by staff and the Peer Review Panel to be scientifically acceptable and soundly based, the technical reports undergo a final technical and style edit prior to printing and distribution. The recommendations of the reviewers and summary comments recorded at the meeting are incorporated where appropriate and relevant in the final revision of the report. Draft summary minutes for each report review are sent to the reviewers for corrections. Edited minutes are made available for distribution to any interested party.

Meetings to perform peer review of NTP draft technical reports are held three times yearly, usually in Research Triangle Park, N.C. A list of the reports to be reviewed, reviewer assignments, review forms, and other information about a particular meeting are sent to Peer Review Panel members prior to the meeting date. At the same time, notices of the meeting are published in the Federal Register. (CONTACT PERSON: Dr. L. Hart, NIEHS)

Tracking of Chemical Testing Status -- An on-line computer data base system (called CHEMTRACK) has been developed for tracking chemicals in various stages of toxicology and carcinogenicity testing. A report was developed which describes the status of NTP chemicals in the various stages of each test program. This report is distributed quarterly on an individual basis to those who want to know about progression of chemicals through the Program. (CONTACT PERSONS: Ms. F. Jordan, and Mr. M. Rowley, NIEHS)

Among the activities of the NLM/NTP information group related to chemical tracking in FY 1984 were the following:

A "Master List of Chemicals of Concern as Possible Carcinogens," which will list chemicals regulated by U.S. agencies as carcinogens or which are under consideration for possible regulation, is being constructed for NTP at ORNL under NLM direction. Printed listings were prepared in FY 1983. (CONTACT PERSON: Dr. P. Craig, NLM, and Mr. J. Wassom, ORNL)

International Coordination -- In partnership with the international community, the NTP strives to formulate a universally-based communication network of toxicologic information, and in particular, in the area of chemical carcinogenesis. Concomitantly, the NTP is seeking active participation from toxicologists and other agencies throughout the world. For instance, contacts have been established with the World Health Organization (WHO), with the International Program on Chemical Safety (IPCS), with the International Agency for Research on Cancer (IARC), with the International Registry of Potentially Toxic Chemicals (IRPTC), with the United Nations Environment Program (UNEP), with the European Chemical Industry Ecology and Toxicology Center (ECETOX), and with governments and individual scientists throughout the world. As an example, in July 1981, an agreement still in existence was entered into with the IARC to establish and maintain an international registry of persons exposed to phenoxy herbicides and contaminants, particularly the chlorinated dibenzodioxins and dibenzofurans. This registry complements the national effort under the guidance of NIOSH. (CONTACT PERSON: Dr. J. Huff, NIEHS)

AN NTP/EPA interagency effort has been continued to maintain a worldwide clearinghouse on phthalate research activities. Information is being collected, catalogued, and stored, primarily about ongoing research and testing efforts; an international registry of scientists engaged in phthalates research is being assembled, and in certain voluntary instances preliminary or recently completed research and testing results will be received and made available. (CONTACT PERSON: Ms. F. Jordan, NIEHS)

Public Information Office (PIO) -- The PIO manages NTP press and public affairs, provides writing and editorial services for the NTP and NIEHS, produces and distributes publications, and conducts public outreach activities. For example, a portable NTP exhibit was displayed at the annual meetings of the Teratology Society in Boca Raton, Florida, on June 24 to 29, and the Industrial Union Department, AFL-CIO, in Hollywood, Florida, on October 3 and 4, 1984.

The PIO also maintain the mailing list for the following:

- NTP Annual Plan (including Part II, Review of Current DHHS, DOE, and EPA Research Related to Toxicology);
- NTP Technical Bulletin;
- Technical Reports on NTP toxicology and carcinogenesis studies;
- Annual Report on Carcinogens, prepared by the NTP for the Secretary of DHHS. A condensed version of the Third Annual Report was prepared by the PIO and distributed to the mailing list in 1983;
- A 17-page pamphlet describing the NTP's mission and structure in general terms.

Questions about the NTP and requests for publications or inclusion on the mailing list should be directed to: NTP Public Information Office, MD B2-04, Box 12233, Research Triangle Park, N.C. 27709. Phone: (919) 541-3991. FTS: 629-3991. (CONTACT PERSON: Ms. F. J. Suttles)

ANNUAL REPORT ON CARCINOGENS

The Fourth Annual Report on Carcinogens is being prepared by the NTP staff and its member agencies for the Secretary, DHHS, pursuant to a 1978 amendment [Section 301 (b) (4)] to the Public Health Service Act which requires that the Secretary, Department of Health and Human Services, publish annually a list of "all substances which are either known to be carcinogens or which may reasonably be anticipated to be carcinogens and to which a significant number of persons residing in the United States are exposed...." Each annual report also contains available information on the nature and degree of exposures to such carcinogens and on the extent of Federal regulations.

The information provided in the Fourth Annual Report on Carcinogens will be developed by the following regulatory and research agencies: the Centers for Disease Control/National Institute for Occupational Safety and Health; the Consumer Product Safety Commission; the Environmental Protection Agency; the Food and Drug Administration; the National Institutes of Health/National Cancer Institute; the National Institutes of Health/National Institute of Environmental Health Sciences; the National Institutes of Health/National Library of Medicine; and the Department of Labor/Occupational Safety and Health Administration.

The Fourth Annual Report on Carcinogens will include the 117 entries in the Third Annual Report as well as information on additional substances, chemicals, or manufacturing processes. These have been selected from among those substances, chemicals, or processes: (1) for which the International Agency for Research on Cancer (IARC) has determined there is sufficient or limited evidence of carcinogenicity in humans or sufficient evidence of carcinogenicity in experimental animals; (2) that are regulated by the Federal government as carcinogens; (3) that have been found to cause cancer in long-term studies conducted by the National Cancer Institute or the NTP; or (4) that have been suggested for inclusion by the agencies involved in preparing the Annual Report.

Each of the entries includes: summaries on the human or animal evidence for carcinogenicity; data on production, occurrence and use; and information on the route and amount of human exposure. The specific regulations promulgated by various Federal agencies are included as well. The report also contains a list of the common synonyms for the chemicals included, a glossary of terms and acronyms and, as required by law, a list of requests to the Department of Health and Human Services for information about carcinogens. (CONTACT PERSON: Dr. R. Shapiro, NIEHS)

When available, copies of the summary of the Fourth Annual Report on Carcinogens will be sent to the mailing list, and, otherwise may be obtained without charge by contacting:

NTP Public Information Office
MD B2-04
P.O. Box 12233
Research Triangle Park, NC 27709
Telephone: (919) 541-3991; FTS 629-3991

Copies of the complete Fourth Annual Report on Carcinogens will be made available for a fee from the National Technical Information Service (NTIS), U. S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161, Telephone: (703) 487-4650.

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APPENDICES

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APPENDIX A

National Toxicology Program
Agency Contacts

Program Management

NTP

Dr. David P. Rall, Director

NCTR

Dr. Ronald W. Hart, Director

NIEHS

Dr. Ernest E. McConnell, Acting Director, Toxicology Research and Testing Program

NIOSH

Dr. Barry L. Johnson, Director, Division of Biomedical and Behavioral Science

Contact Persons

The following alphabetical list includes NTP agency program leaders, project officers, and other key agency staff who should be contacted for further information about activities described in this NTP Annual Plan for FY 1985.

Name	Agency/Location*	Telephone Numbers**
Dr. Kamal Abdo	NIEHS/NC	541-7819 629-7819
Dr. William Allaben	NCTR	541-4211 790-4211
Dr. Kent Anger	NIOSH/OH	533-8383 684-8383
Dr. Linda Birnbaum	NIEHS/NC	541-3583 629-3583
Dr. Jeffrey Bohrman	NIOSH/OH	533-8357 684-8357
Dr. Lawrence R. Boone	NIEHS/NC	541-3987 629-3987

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APPENDIX A (Continued)

Name	Agency/Location*	Telephone Numbers**
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Dr. Douglas Bristol	NIEHS/NC	541-2647 629-2647
Dr. Sandra Brown	NIEHS/AZ	629-6000 762-6000
Dr. John Bucher	NIEHS/NC	541-4532 629-4532
Ms. Judy Bulke-Sam	NCTR	541-4066 790-4066
Dr. Dorothy Canter	NIEHS/MD	496-3511
Dr. Daniel Casciano	NCTR	541-4496 790-4496
Dr. William Caspary	NIEHS/NC	541-2150 629-2150
Dr. PO Cheun Chan	NIEHS/NC	541-3386 629-3386
Dr. Robert Chapin	NIEHS/NC	541-3742 629-3742
Mr. Kenneth Cheever	NIOSH/OH	533-8497 684-8497
Dr. Rajendra Chhabra	NIEHS/NC	541-3386 629-3386
Dr. Jeffrey J. Collins	NIEHS/NC	541-2264 629-2264
Dr. Paul Craig	NLM	496-6531
Mr. Gerald Cronin	NCTR	541-4046 790-4046
Dr. F. Bernard Daniel	NIOSH/OH	533-8496 684-8496
Dr. Robert Dick	NIOSH/OH	533-8383 684-8383
Dr. Michael Dieter	NIEHS/NC	541-3368 629-3368

APPENDIX A (Continued)

Name	Agency/Location*	Telephone Number**
Dr. Gregg Dinse	NIEHS/NC	541-4931 629-4931
Dr. June Dunnick	NIEHS/NC	541-4811 629-4811
Dr. William Eastin	NIEHS/NC	541-7941 629-7941
Dr. Lawrence Fishbein	NCTR	541-4390 790-4390
Dr. John French	NIEHS/NC	541-7790 629-7790
Dr. David Gaylor	NCTR	541-4001
Dr. Craig Giroux	NIEHS/NC	541-5013 629-5013
Dr. Thomas Goehl	NIEHS/NC	541-7961 629-7961
		542-4001
Dr. Joyce Goldstein	NIEHS/NC	541-4495 629-4495
Mr. Gary Green	NCTR	541-4534 790-4534
Dr. Bhola Gupta	NIEHS/NC	541-3233 629-3233
Dr. Brian Hardin	NIOSH/OH	533-8394 684-8394
Dr. Larry Hart	NIEHS/NC	541-3971 629-3971
Dr. Ronald Hart	NCTR	541-4517 790-4517
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APPENDIX A (Continued)

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APPENDIX A (Continued)

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APPENDIX A (Continued)

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APPENDIX A (Continued)

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NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF A POLYBROMINATED BIPHENYL MIXTURE (FIREMASTER FF-1) (CAS NO. 67774-32-7) IN F344/N RATS AND B6C3F1 MICE (GAVAGE STUDIES)
NTP - NIH PUBLICATION NO. 83-1800
NTP-81-032 TR-244 P PUBLISHED 83 PB83240473

GUPTA BN (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE CARCINOGENESIS STUDIES OF
ETHOXYLATED DODECYL ALCOHOL (CAS NO. 9002-92-0) IN F344/N
RATS AND B6C3F1 MICE (FEED STUDY)
NTP - NIH PUBLICATION NO. 84-2520
NTP-82-093 TR-264 CAMERA TJ 831219

HUFF JE (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE CARCINOGENESIS STUDIES OF
C.I. ACID ORANGE 10 (CAS NO. 1936-15-8) IN F344/N RATS AND
B6C3F1 MICE (FEEDING STUDIES)
NTP - NIH PUBLICATION NO. 84-1767
NTP-80-030 TR-211 CAMERA 2 NTP 840503

HUFF JE (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE CARCINOGENESIS STUDIES OF
EUGENOL (CAS NO. 97-53-0) IN F344/N RATS AND B6C3F1 MICE
(FEED STUDIES)
NTP - NIH PUBLICATION NO. 83-1779
NTP-80-068 TR-223 P PUBLISHED 8312 PB84186402

HUFF JE (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE CARCINOGENESIS STUDIES OF
ALLYL ISOVALERATE (CAS NO. 2835-39-4) IN F344/N RATS AND
B6C3F1 MICE (GAVAGE STUDY)
NTP - NIH PUBLICATION NO. 82-2509
NTP-82-004 TR-253 P PUBLISHED 83 PB83218214

HUFF JE (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS OF
BENZENE (CAS NO. 71-43-2) IN F344/N RATS AND B6C3F1 MICE
(GAVAGE STUDY)
NTP - NIH PUBLICATION NO. 84-2545
NTP-83-072 TR-289 BSC NTP 840718

IRWIN RD (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE CARCINOGENESIS BIOASSAY OF
SODIUM 2-ETHYLHEXYL SULFATE (CAS NO. 126-92-1) IN F344/N
RATS AND B6C3F1 MICE (FEED STUDY)
NTP - NIH PUBLICATION NO. 82-2512
NTP-82-063 TR-256 CAMERA NTP 840113

IRWIN RD (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS
STUDIES OF SODIUM DODECYL SULFATE (CAS NO. 151-21-3) IN F344/N
RATS AND B6C3F1 MICE (FEED STUDIES) SODIUM DODECYL
SULFATE (CAS NO. 151-21-3) IN F344/N RATS AND B6C3F1 MICE
(FEED STUDY)
NTP - NIH PUBLICATION NO. 84-2524
NTP-83-021 TR-268 STAFF NTP 840813

JAMESON CW (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS
STUDIES OF TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM SULFATE (THPS)
IN F344/N RATS AND B6C3F1 MICE (GAVAGE STUDIES)
NTP - NIH PUBLICATION NO. 84-2552
NTP-83-266 TR-296 II & III NTP 831125

KLUWE WM (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE CARCINOGENESIS STUDIES OF
CHLOROBENZENE (CAS NO. 108-90-7) IN F344/N RATS AND B6C3F1
MICE (GAVAGE STUDIES)
NTP - NIH PUBLICATION NO. 83-2517
NTP-82-090 TR-261 CAMERA TJ 831219

KLUWE WM (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS
STUDIES OF DIALLYLPHTHALATE (CAS NO. 131-17-9) IN F344/N RATS
(GAVAGE STUDY)
NTP - NIH PUBLICATION NO. 84-2540
NTP-83-047 TR-284 GALLEY NTP 841010

LAMB JC (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE CARCINOGENESIS STUDIES OF
1,2-DICHLOROPROPANE (PROPYLENE DICHLORIDE) (CAS NO. 78-87-5)
IN F344/N RATS AND B6C3F1 MICE (GAVAGE STUDY)
NTP - NIH PUBLICATION NO. 83-2519
NTP-82-092 TR-263 CAMERA NTP 831223

MARONPOT RR (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE CARCINOGENESIS BIOASSAY OF
ETHYL ACRYLATE (CAS NO. 140-88-5) IN F344/N RATS AND B6C3F1
MICE (GAVAGE STUDY)
NTP - NIH PUBLICATION NO. 83-2515
NTP-82-077 TR-259 P PUBLISHED 8308

MATTHEWS HB (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS
STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE (CAS NO. 78-42-2) IN
F344/N RATS AND B6C3F1 MICE (GAVAGE STUDIES) TRIS(2-
ETHYLHEXYL)PHOSPHATE (CAS NO. 78-42-2) IN F344/N RATS AND
B6C3F1 MICE (GAVAGE STUDY)
NTP - NIH PUBLICATION NO. 84-2530
NTP-83-027 TR-274 P PUBLISHED 8408

MCCONNELL EE (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE CARCINOGENESIS LIFETIME STUDIES OF
CHRYSOTILE ASBESTOS (CAS NO. 12001-29-5) IN SYRIAN GOLDEN
HAMSTERS (FEED STUDY)
NTP - NIH PUBLICATION NO. 82-2502
NTP-81-051 TR-246 CAMERA JC 831130

MCCONNELL EE (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE LIFETIME CARCINOGENESIS STUDIES OF
AMOSITE ASBESTOS (CAS NO. 12172-73-5) IN SYRIAN GOLDEN
HAMSTERS (FEED STUDIES)
NTP - NIH PUBLICATION NO. 84-2505
NTP-81-058 TR-249 P PUBLISHED 8311

MCCONNELL EE (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE CARCINOGENESIS STUDIES OF
DIGLYCIDYL RESORCINOL ETHER (TECHNICAL GRADE) (CAS NO. 101-
90-6) IN F344/N RATS AND B6C3F1 MICE (GAVAGE STUDIES)
NTP - NIH PUBLICATION NO. 84-2513
NTP-82-064 TR-257 CAMERA TJ 831219

MCCONNELL EE (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS
STUDIES OF CHRYSOTILE ASBESTOS (CAS NO. 12001-29-5) IN F344/N
RATS (FEED STUDIES)
NTP - NIH PUBLICATION NO. 84-2551
NTP-83-173 TR-295 RSC NTP 840718

MELNICK RL (CHEMICAL MANAGER)
NTP TOXICOLOGY AND CARCINOGENISIS STUDIES OF
1,2-EPOXYHEXADECANE (CAS NO. 7320-37-8) IN F344/N RATS AND
B6C3F1 MICE (DERMAL STUDIES)
NTP - NIH PUBLICATION
NTP-84-132 TR-302 II & III NTP 840726

MENNEAR JH (CHEMICAL MANAGER)
FURTHER STUDIES ON THE HEPATOCARCINGENICITY OF
TETRACHLOROETHYLENE (CAS NO. 127-18-4) IN FEMALE B6C3F1 MICE
(GAVAGE STUDIES)
NTP - NIH PUBLICATION NO. 84-2516
NTP-82-067 TR-260 STAFF REVD 840413

MENNEAR JH (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS
STUDIES OF HC BLUE NO. 1 (CAS NO. 2784-94-3) IN F344/N RATS
AND B6C3F1 MICE (FEED STUDIES)
NTP - NIH PUBLICATION NO. 84-2527
NTP-83-024 TR-271 GALLEY NTP 840821

MENNEAR JH (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS
STUDIES OF TECHNICAL GRADE (75 TO 90% PURE) FLUORESCEIN
SODIUM (C.I. ACID YELLOW 73) (CAS NO. 518-47-8) IN F344/N RATS
AND B6C3F1 MICE (DRINKING WATER STUDIES)
NTP - NIH PUBLICATION NO. 83-2521
NTP-83-018 TR-265 GALLEY NTP 831118

MENNEAR JH (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICITY AND CARCINOGENICITY OF
TRICHLOROETHYLENE (CAS NO. 79-01-6) IN ACI, AUGUST,
MARSHALL, AND OSBORNE-MENDEL RATS (GAVAGE STUDY)
NTP - NIH PUBLICATION NO. 83-2529
NTP-83-026 TR-273 II & III NTP 840409

MENNEAR JH (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS
STUDIES OF HC RED NO. 3 (CAS NO. 2871-01-4) IN F344/N RATS AND
B6C3F1 MICE (GAVAGE STUDIES) HC RED NO. 3 (CAS NO. 2871-01-4)
IN F344/N RATS AND B6C3F1 MICE (GAVAGE STUDY)
NTP - NIH PUBLICATION NO. 85-2537
NTP-83-046 TR-281 STAFF2 NTP 841217

MENNEAR JH (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS
STUDIES OF HC BLUE NO. 2 2,2'-(4-(2-HYDROXYETHYL)AMINO)-3-
NITROPHENYL)MINO)BIS(ETHANOL) IN F344/N RATS AND B6C3F1 MICE
(FEED STUDIES) HC BLUE NO. 2 (CAS NO. 33229-34-4) IN F344/N
RATS AND B6C3F1 MICE (FEED STUDIES)
NTP - NIH PUBLICATION NO. 84-2549
NTP-83-170 TR-293 GALLEY NTP 841010

MONTGOMERY CA (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS
STUDIES OF 2,6-XYLIDINE (2,6-DIMETHYLANILINE) (CAS NO. 87-62-
7) IN CHARLES RIVER CD RATS (FEED STUDIES)
NTP - NIH PUBLICATION NO. 84-2534
NTP-82-094 TR-278 GALLEY NTP 831221

POWERS MB (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS
STUDIES OF 1,3-BUTADIENE (CAS NO. 106-99-0) IN B6C3F1 MICE
(INHALATION STUDIES) 1,3-BUTADIENE (CAS NO. 106-99-0) IN
B6C3F1 MICE (INHALATION STUDIES)
NTP - NIH PUBLICATION NO. 84-2544
NTP-83-071 TR-288 PUBLISHED 8408

QUEST JA
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS
STUDIES OF PROPYLENE (CAS NO 115-07-1) IN F344/N RATS AND
B6C3F1 MICE (INHALATION STUDY)
NTP - NIH PUBLICATION NO. 85-2528
NTP-83-025 TR-272 CAMERA NTP 841217

RAUCKMAN E (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF C.I. DISPERSE BLUE 1 (CAS NO. 2475-45-8) IN F344/N RATS AND B6C3F1 MICE (FEED STUDIES)
NTP - NIH PUBLICATION NO. 85-2555
NTP-84-034 TR-299 PREL NTP 841121

THADANI PS (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF HAMAMELIS WATER IN F344/N RATS AND B6C3F1 MICE (DERMAL STUDIES)
NTP - NIH PUBLICATION NO. 84-2542
NTP-83-062 TR-286 GALLEY NTP 840523

WHITMIRE CE (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLORINATED TRISODIUM PHOSPHATE (CAS NO. 56802-99-4) IN B6C3F1 MICE (GAVAGE STUDIES)
NTP - NIH PUBLICATION NO. 84-2550
NTP-83-171 TR-294 BOARD MTG 841102

YANG RSH (CHEMICAL MANAGER)
NTP TECHNICAL REPORT ON THE CARCINOGENESIS STUDIES OF TELONE II(R) (TECHNICAL GRADE 1,3-DICHLOROPROPENE (CAS NO. 542-75-6) CONTAINING 1.0% EPICHLOROHYDRIN AS A STABILIZER) IN F344/N RATS AND B6C3F1 MICE (GAVAGE STUDIES)
NTP - NIH PUBLICATION NO. 84-2525
NTP-83-022 TR-269 BSC NTP 840718

* ALSO INCLUDES EARLIER PUBLICATIONS OMITTED FROM PREVIOUS NTP ANNUAL PLANS, AS WELL AS PUBLICATIONS PREVIOUSLY LISTED FOR WHICH A COMPLETE CITATION WAS NOT AVAILABLE.

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INDEXES

3/3

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INTRODUCTION TO INDEXES

The indexes are organized as in the FY 1985 NTP Annual Plan. There are two indexes: Chemical Index (by name) and CAS Registry Number Index. The Chemical Index is arranged by a straight alphabetical sort which ignores single letters, most prefixes and numbers in sequencing the names, e.g. beta-cadinene is sorted under C; p-nitroaniline is under N; N,N-dimethylaniline is under D; and 2,4-dinitrotoluene is under D. Certain colors may be listed under more than one name, e.g., C.I. Direct Blue 6 or Direct Blue 6.

Please note that under "Page/Seq" when two numbers are given the first number refers to the exact page of the table in which the chemical is found, while the second number refers to the sequence within the table. For example, 69/079 tells us that carminic acid is on page 69 where it is the 79th chemical entry in Table 2 (Table 2 begins on page 68); while, 110/104 tells us that nalidixic acid is on page 110 where it is the 104th chemical entry in Table 11 which begins on page 105. When only one number is given, preceded by a "P", e.g., P/131, this means the chemical mentioned in the text as in this case on page 131.

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
ACETALDEHYDE	87/001
ACETALDEHYDE	198/001
ACETAMINOPHEN	105/001
ACETAMINOPHEN	117/001
ACETIN	87/002
ACETONE	P/180
ACETONE	198/002
ACETONITRILE	166/001
2-ACETYLAMINOFLUORENE	P/48
2-ACETYLAMINOFLUORENE	P/56
2-ACETYLAMINOFLUORENE	P/135
4-ACETYLAMINOFLUORENE	P/56
4-ACETYLAMINOFLUORENE	80/001
4-ACETYLAMINOFLUORENE	82/001
2-ACETYLAMINO-4-METHYLPHENOL	68/001
N-ACETYL-M-AMINOPHENOL	68/002
1-ACETYL-2-PHENYL HYDRAZIDE	63/001
ACETYLSALICYLIC ACID	68/003
N-ACETYL-M-TOLUIDINE	68/004
N-ACETYL-P-TOLUIDINE	68/005
ACID BLACK 52	P/31
ACID BLACK 52	P/125
ACID BLACK 52	P/127
ACROLEIN	P/170
ACROLEIN	P/184
ACROLEIN	78/001
ACROLEIN IN NITROGEN	235/001
ACRYLAMIDE	P/178
ACRYLAMIDE	P/179
ACRYLAMIDE	P/192
ACRYLAMIDE	63/002
ACRYLATE ESTERS	P/143
ACRYLONITRILE	P/56
ACRYLONITRILE	79/001
ADIPONITRILE	68/006
AFLATOXIN EXTRACT AA 34-1	63/003
AFLATOXIN EXTRACT AA 34-2	63/004
AFLATOXIN EXTRACT AA 34-4	63/005
AFLATOXIN EXTRACT AA 34-5	63/006
AFLATOXIN EXTRACT AA 34-6	63/007
AFLATOXIN EXTRACT AA 34-7	63/008
AFLATOXIN EXTRACT AA 34-8	63/009
AFLATOXIN EXTRACT AA 34-9	63/010
AGARITINE	68/007
ALDICARB	68/008
ALDICARB	85/001
ALLOXAN	68/009
ALLOXAN MONOHYDRATE	68/010
ALLOXAN MONOHYDRATE	87/003
ALLYL ACRYLATE	63/011
ALLYLAMINE	P/137
ALLYL CHLORIDE	197/001
ALLYL GLYCIDYL ETHER	85/002
ALLYL GLYCIDYL ETHER	105/002
ALLYL ISOTHIOCYANATE	P/149
ALLYL ISOTHIOCYANATE	82/002
ALLYL ISOVALERATE	85/003
ALLYLTHIOUREA	68/011
ALUMINUM SILICATES	P/125
AMILORIDE HCL	68/012
2-AMINOACETANILIDE	68/013
M-AMINOACETANILIDE	63/013
P-AMINO ACETANILIDE	63/012
9-AMINOACRIDINE	P/44
9-AMINOACRIDINE	196/006
9-AMINOACRIDINE HCL H2O	85/004
9-AMINOACRIDINE HYDROCHLORIDE	P/144
9-AMINOACRIDINE HYDROCHLORIDE	104/001
9-AMINOACRIDINE HYDROCHLORIDE	233/001
2-AMINOANTHRACENE	87/004
5-(4-AMINOBENZAMIDO)-2,3-CRESOTIC ACID	68/014
2-AMINOBENZENESULFONIC ACID	68/015
3-AMINOBENZENESULFONIC ACID	68/016
4-AMINOBENZENESULFONIC ACID	68/017
2-AMINOBENZIMIDAZOLE	68/018
2-AMINO-4-CHLORO-6-NITROPHENOL	68/019
2-AMINO-6-CHLORO-4-NITROPHENOL	68/020
2-AMINO-4-CHLOROPHENOL	68/021
6-AMINO-4-CHLORO-1-PHENOL-2-SULFONIC ACID	68/022
1-AMINO-2,4-DIBROMOANTHRAQUINONE	105/003
1-AMINO-2,4-DIBROMOANTHRAQUINONE	117/002
2-AMINO-4,6-DICHLOROPHENOL	68/023
2-AMINO-4,6-DINITROPHENOL	68/024
2-AMINOFLUORENE	P/57
4-AMINO-4'-HYDROXY-3-METHYL-DIPHENYLAMINE	68/025
1-AMINO-2-METHYLANTHRAQUINONE	68/026
2-AMINO-4-METHYLPHENOL	68/027
3-AMINO-4-METHYLPHENOL	68/029
3-AMINO-6-METHYLPHENOL	68/028
2-AMINO-4-(METHYLSULFONYL)PHENOL	68/030
2-AMINO-3-NITRO-4-METHYLPHENOL	68/032
2-AMINO-5-NITRO-4-METHYLPHENOL	68/031
2-AMINO-4-NITROPHENOL	80/002
2-AMINO-4-NITROPHENOL	105/004
2-AMINO-5-NITROPHENOL	105/005
4-AMINO-2-NITROPHENOL	63/014
2-AMINO-6-NITRO-1-PHENOL-4-SULFONIC ACID	68/034
6-AMINO-4-NITRO-1-PHENOL-2-SULFONIC ACID	68/033
2-AMINO-5-NITROTHIAZOLE	P/131
4-AMINOPHENOL	63/015
O-AMINOPHENOL	210/001
P-AMINOPHENOL	210/004
O-AMINOPHENOL HYDROCHLORIDE	210/002
P-AMINOPHENOL HYDROCHLORIDE	210/005
O-AMINOPHENOL SULFATE	210/003
P-AMINOPHENOL SULFATE	210/006
2-AMINO-1-PHENOL-4-SULFONIC ACID	68/035
3-AMINO-5-SULFOSALICYLIC ACID	68/037
5-AMINO-3-SULFOSALICYLIC ACID	68/036
3-AMINOTRIAZOLE	68/038
3-AMINOTRIAZOLE	80/003
3-AMINOTRIAZOLE	82/003
3-AMINOTRIAZOLE	87/005
2-AMINO-3,4,6-TRICHLOROPHENOL	68/039
11-AMINOUNDECANOIC ACID	P/131
11-AMINOUNDECANOIC ACID	82/004
AMPHETAMINE SULFATE	79/002
AMPHETAMINE SULFATE	105/006
AMPHOTERICIN B	68/040
AMPICILLIN TRIHYDRATE	80/004
AMPICILLIN TRIHYDRATE	87/006
AMPICILLIN TRIHYDRATE	105/007
AMPICILLIN TRIHYDRATE	163/001
AMPICILLIN TRIHYDRATE	164/001
ANILAZINE	68/041
ANILAZINE	85/005
ANILINE	80/005
O-ANTHRANILIC ACID	85/006
ANTHRAQUINONE	68/042
ANTIMONY POTASSIUM TARTATE	220/001
AROCLOR 1254	68/043
AROCLOR 1254	P/131
ARSENIC	P/127
ARSENIC TRIOXIDE	212/032
ARSINE	215/001
ARSINE	220/002
ASBESTOS CHRYSOTILE	P/156
ASBESTOS CHRYSOTILE	P/161
ASBESTOS, CHRYSOTILE	98/001
ASBESTOS CHRYSOTILE	164/002

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
ASBESTOS FIBERS	P/31
ASBESTOS FIBERS	P/124
ASBESTOS FIBERS	P/127
L-ASCORBIC ACID	82/005
ASPARTAME	212/033
ASPHALT	P/126
ASPHALT FUMES	P/126
ASPHALTS	P/151
ATRAZINE	68/044
ATRAZINE	219/007
5-AZACYTIDINE	68/045
5-AZACYTIDINE	87/007
AZATHIOPRINE	68/046
AZINPHOSMETHYL	63/016
1-AZIRIDINEETHANOL	87/008
AZODICARBONAMIDE	P/149
AZODICARBONAMIDE	85/007
AZODICARBONAMIDE	114/001
AZOXYMETHANE	69/047
BARIUM CHLORIDE DIHYDRATE	69/048
BARIUM CHLORIDE DIHYDRATE	82/006
BARIUM CHLORIDE DIHYDRATE	85/008
BARIUM CHLORIDE DIHYDRATE	166/002
BENDECTIN	194/001
BENDECTIN	P/188
BENOMYL	69/049
BENZALDEHYDE	78/002
BENZALDEHYDE	80/006
BENZALDEHYDE	105/008
BENZALDEHYDE	198/003
BENZAMIDE	63/017
BENZENE	P/44
BENZENE	P/50
BENZENE	P/56
BENZENE	P/170
BENZENE	80/007
BENZENE	98/002
BENZENE	163/002
BENZENE	164/003
BENZENE SULFONIC ACID	69/050
BENZETHONIUM CHLORIDE	P/44
BENZETHONIUM CHLORIDE	85/009
BENZETHONIUM CHLORIDE	114/002
BENZETHONIUM CHLORIDE	198/004
BENZIDINE	P/23
BENZIDINE	P/57
BENZIDINE	P/138
BENZIDINE	P/172
BENZIDINE	P/173
BENZIDINE	140/001
BENZIDINE	176/005
BENZIMIDAZOLE	69/051
BENZIMIDAZOL-2-YLUREA	69/052
BENZOFURAN	80/008
BENZOFURAN	105/009
BENZOIC ACID	69/053
BENZOIN	P/56
BENZONITRILE	63/018
BENZONITRILE	114/003
BENZONITRILE	223/001
BENZO(A)PYRENE	P/48
BENZO(A)PYRENE	P/56
BENZO(A)PYRENE	P/57
BENZO(A)PYRENE	P/125
BENZO(A)PYRENE	79/003
BENZO(A)PYRENE	87/009
BENZO(E)PYRENE	69/054
BENZO(F)QUINOLINE	P/148
BENZO(F)-QUINOLINE	63/019
BENZO(F)-QUINOLINE	114/004
BENZO(F)QUINOLINE	223/002
BENZOTRIAZOLE	69/055
BENZOYL CHLORIDE	69/056
BENZOYL CHLORIDE	P/44
BENZOYL PEROXIDE	63/020
BENZYL ACETATE	P/44
BENZYL ACETATE	P/142
BENZYL ACETATE	82/007
BENZYL ACETATE	105/010
BENZYL ACETATE	114/005
BENZYL ACETATE	163/003
BENZYL ACETATE	164/004
BENZYL ALCOHOL	80/009
BENZYL ALCOHOL	85/010
BENZYL ALCOHOL	105/011
BENZYL ALCOHOL	198/005
BENZYL CHLORIDE	63/021
BENZYL CHLORIDE	80/010
BENZYL CHLORIDE	87/010
BENZYL CHLORIDE	118/001
O-BENZYL-P-CHLOROPHENOL	P/148
O-BENZYL-P-CHLOROPHENOL	104/002
O-BENZYL-P-CHLOROPHENOL	116/001
O-BENZYL-P-CHLOROPHENOL	116/002
O-BENZYL-P-CHLOROPHENOL	166/003
BENZYLTRIMETHYL AMMONIUM CHLORIDE	63/022
BERYLLIUM SULFATE TETRAHYDRATE	69/057
2-BIPHENYLAMINE	63/023
2-BIPHENYLAMINE	P/131
2-BIPHENYLAMINE HYDROCHLORIDE	82/008
2,4-BIS(P-AMINOBENZYL) ANILINE	63/024
1,3-BIS(2-BENZOTHIAZOLYLMERCAPTO-METHYL) UREA	63/025
2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL	P/169
2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL	166/004
2,2'-BIS(BROMOMETHYL) 1,3-PROPANEDIOL	196/007
2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL	233/002
1,3-BIS(TERT-BUTYLDIOXYISOPROPYL) BENZENE	69/058
BIS T-BUTYLDIOXYISOPROPYLBENZENE	69/062
BIS(2-CHLOROETHYL)ETHER	79/004
BIS(2-CHLORO-1-METHYLETHYL) ETHER	82/009
BIS(1,5-CYCLOOCTADIENE) NICKEL	69/059
BIS(CYCLOPENTADIENYL)VANADIUM CHLORIDE	69/060
BIS [2-METHYOXYETHYL] ETHER	P/151
BIS(2-ETHYLHEXYL)ISOPHTHALATE	69/061
BISPHENOL A	82/010
BISPHENOL A	194/002
BISPHENOL A	195/001
BISPHENOL A	196/008
BISPHENOL A	233/003
BISPHENOL A DIGLYCIDYL ETHER	85/011
BISPHENOL A DIGLYCIDYL ETHER	87/011
(4,4'-BITHIAZOLE)-2,2'-DIAMINE	69/063
BIUREA	69/064
BIUREA	87/012
BLACK NEWSPRINT INKS	P/203
BLACK NEWSPRINT INKS	P/204
BLACK NEWSPRINT INKS	215/002
BLACK NEWSPRINT INKS	220/003
BORIC ACID	82/011
BORIC ACID	85/012
BORIC ACID	105/012
BROMOBENZENE	104/003
BROMOBENZENE	104/004
BROMOBENZENE	P/44
BROMOCHLOROACETALDEHYDE	69/065
BROMOCHLOROACETONITRILE	69/066
BROMOCHLOROACETONITRILE	211/019
BROMODICHLOROMETHANE	80/011
BROMODICHLOROMETHANE	85/013
BROMODICHLOROMETHANE	105/013
BROMODICHLOROMETHANE	163/004
2-BROMO-1-ETHANOL	63/026

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
2-BROMOETHYL ACRYLATE	63/027
BROMOFORM	78/003
BROMOFORM	80/012
BROMOFORM	105/014
BETA-BROMO-BETA-NITROSTYRENE	63/028
BROMOPICRIN	69/067
1-BROMO-2-PROPANOL	69/068
1,3-BUTADIENE	P/22
1,3-BUTADIENE	P/23
1,3-BUTADIENE	P/44
1,3-BUTADIENE	P/96
1,3-BUTADIENE	P/133
1,3-BUTADIENE	P/173
1,3-BUTADIENE	69/069
1,3-BUTADIENE	79/005
1,3-BUTADIENE	87/013
1,3-BUTADIENE	99/003
1,3-BUTADIENE	114/006
1,3-BUTADIENE	116/003
1,3-BUTADIENE	164/005
1,3-BUTADIENE	234/001
N-BUTANE	212/034
1,4-BUTANEDIOL DIGLYCIDYL ETHER	79/006
2-BUTANOL	P/181
N-BUTANOL	P/180
2-BUTANONE PEROXIDE	80/013
2-BUTANONE PEROXIDE	87/014
2-BUTANONE PEROXIDE	105/015
2-BUTOXYETHANOL	211/013
2-BUTOXYETHANOL	P/151
2-BUTOXYETHANOL ACETATE	211/014
2-(2-BUTOXYETHOXY)ETHYL THIOCYANATE	69/070
2-(2-BUTOXYETHOXY)ETHYL THIOCYANATE	220/004
N-BUTYL ACRYLATE	212/035
t-BUTYL ALCOHOL	167/003
t-BUTYL ALCOHOL	167/002
t-BUTYL ALCOHOL	167/001
TERT-BUTYL ALCOHOL	80/014
TERT-BUTYL ALCOHOL	85/014
TERT-BUTYL ALCOHOL	105/016
BUTYLATED HYDROXYTOLUENE	82/012
BUTYLATED HYDROXYTOLUENE	P/230
BUTYL BENZYL PHTHALATE	P/185
BUTYL BENZYL PHTHALATE	P/186
BUTYL BENZYL PHTHALATE	82/013
BUTYL BENZYL PHTHALATE	104/005
BUTYL BENZYL PHTHALATE	164/006
BUTYL BENZYL PHTHALATE	223/003
N-BUTYL CHLORIDE	80/015
N-BUTYL CHLORIDE	85/015
N-BUTYL CHLORIDE	105/017
N-BUTYL CHLORIDE	105/018
N-BUTYL CHLORIDE	163/005
n-BUTYL CHLORIDE	164/007
TERT-BUTYL CHROMATE	69/071
N-BUTYL GLYCIDYL ETHER	69/072
T-BUTYL GLYCIDYL ETHER	69/073
TERT-BUTYL HYDROPEROXIDE	85/016
t-BUTYL PERBENZOATE	P/143
TERT-BUTYL PERBENZOATE	87/015
TERT-BUTYL PERBENZOATE	114/007
T-BUTYL PHENYL GLYCIDYL ETHER	69/074
BUTYLTIN-TRIS(ISOOCTYLMERCAPTOACETATE)	63/030
BUTYRALDEHYDE	114/008
BUTYRALDEHYDE	114/009
BUTYRALDEHYDE	198/006
BUTYRIC ACID	69/075
GAMMA-BUTYROLACTONE	87/016
GAMMA-BUTYROLACTONE	105/019
CADMIUM	P/151
CADMIUM CHLORIDE	P/182
CADMIUM CHLORIDE	82/014
CADMIUM CHLORIDE	176/001
CADMIUM CHLORIDE	234/002
CAFFEINE	P/119
CAFFEINE	P/120
CAFFEINE	166/005
CAFFEINE	195/002
CAFFEINE	195/003
CAFFEINE	196/001
CAFFEINE	196/023
CALCIUM CHROMATE	63/031
CALCIUM CHROMATE	80/016
CALCIUM CHROMATE	82/015
CALCIUM CHROMATE	87/017
CAPROLACTAM	P/56
CARBARSONE	69/076
4-(3-CARBAZOYLAMINO)PHENOL	69/077
CARBODOX	212/036
CARBON DISULFIDE	P/137
CARBON DISULFIDE	P/170
CARBON DISULFIDE	P/180
CARBON DISULFIDE	P/188
CARBON DISULFIDE	87/018
CARBON DISULFATE	194/003
CARBON TETRACHLORIDE	P/43
CARBON TETRACHLORIDE	P/145
CARBON TETRACHLORIDE	P/180
CARBON TETRACHLORIDE	69/078
CARBROMAL	87/019
CARISOPRODOL	80/017
CARISOPRODOL	85/017
CARMINIC ACID	69/079
D-CARVONE	105/020
D-CARVONE	106/021
CASTOR OIL	63/032
CASTOR OIL	106/022
CATECHOL	212/037
CHLORAL	63/033
CHLORAL HYDRATE	87/020
CHLORAMBEN	87/021
CHLORAMBUCIL	78/004
CHLORAMBUCIL	87/022
CHLORAMINE	P/44
CHLORAMINE	106/023
CHLORAMINE	116/004
CHLORAMPHENICOL SODIUM SUCCINATE	79/007
CHLORDANE (REAGENT GRADE)	85/018
CHLORDANE (TECHNICAL GRADE)	82/016
CHLORDANE (TECHNICAL GRADE)	87/023
CHLORDECONE	P/32
CHLORDECONE	P/177
CHLORDECONE	P/178
CHLORDECONE	P/179
CHLORENDIC ACID	80/018
CHLORENDIC ACID	87/024
CHLORENDIC ACID	106/024
CHLORENDIC ACID	163/006
CHLORINATED BENZENES	P/145
CHLORINATED TRISODIUM PHOSPHATE	63/034
CHLORINATED TRISODIUM PHOSPHATE	87/025
CHLORINATED TRISODIUM PHOSPHATE	106/025
CHLORINATED TRISODIUM PHOSPHATE	164/008
a-CHLOROACETOPHENONE	167/004
CHLOROACETOPHENONE (CN)	106/027
4-(CHLOROACETYL)ACETANILIDE	69/080
4-(CHLOROACETYL)ACETANILIDE	87/026
N-(3-CHLOROALLYL)HEXAMINIUM CHLORIDE	69/081
M-CHLOROANILINE	63/036
P-CHLOROANILINE	63/035
P-CHLOROANILINE	80/020
P-CHLOROANILINE	82/017
P-CHLOROANILINE	106/028
O-CHLOROBENZALMALONONITRILE (CS)	80/021

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
O-CHLOROBENZALMALONONITRILE (CS)	106/029
O-CHLOROBENZALMALONONITRILE (CS)	117/003
CHLOROBENZENE	87/027
CHLOROBENZENE	P/135
CHLOROBENZILATE	80/022
CHLOROBENZILATE	82/018
CHLORODIAZEPOXIDE	210/007
CHLORODIBROMOMETHANE	P/44
CHLORODIBROMOMETHANE	99/004
CHLORODIBROMOMETHANE	164/009
4-CHLORO-2-(2,4-DINITROANILINO)PHENOL	69/082
2-CHLOROETHANOL	P/44
2-CHLOROETHANOL	99/005
2-CHLOROETHANOL	164/010
2-CHLOROETHANOL (ETHYLENE CHLOROHYDRIN)	80/023
2-CHLOROETHANOL (ETHYLENE CHLOROHYDRIN)	85/019
2-CHLOROETHYLTRIMETHYLAMMONIUM CHLORIDE	87/028
CHLOROFORM	P/135
CHLOROFORM	P/184
CHLOROFORM II	163/007
3-CHLORO-2-METHYLPROPENE	87/029
3-CHLORO-2-METHYLPROPENE	106/030
3-CHLORO-2-METHYLPROPENE	163/008
3-CHLORO-2-METHYLPROPENE	164/011
3-CHLOROMETHYLPYRIDINE HYDROCHLORIDE	78/005
3-CHLOROMETHYLPYRIDINE HYDROCHLORIDE	80/024
3-CHLOROMETHYLPYRIDINE HYDROCHLORIDE	82/019
CHLORONEB	69/083
4-CHLORO-2-NITROANILINE	82/020
2-CHLORONITROBENZENE	210/011
4-CHLORONITROBENZENE	210/012
1-CHLORO-1-NITROPROPANE	69/084
2-CHLORO-2-NITRO-PROPANE	69/085
4-CHLORO-O-PHENYLENEDIAMINE	63/037
CHLOROPRENE	87/030
CHLOROPRENE (2-CHLORO-1,3-BUTADIENE)	P/134
2-CHLORO-1,3-PROPANEDIOL	69/086
3-CHLORO-1,2-PROPANEDIOL	63/038
1-CHLORO-2-PROPANOL	69/087
1-CHLORO-2-PROPANOL	79/009
1-CHLORO-2-PROPANOL	223/004
2-CHLORO-1-PROPANOL	69/088
2-CHLORO-1-PROPANOL	223/005
3-CHLORO-1-PROPANOL	69/089
O-CHLOROSTYRENE	69/090
CHLOROTHALONIL	82/021
CHLOROTHIAZIDE	69/091
CHLORO-THIOFORMIC ACID	P/203
CHLOROTHIOFORMIC ACID	69/092
5-CHLORO-O-TOLUIDINE	82/022
P-CHLORO-a,a,a-TRIFLUOROTOLUENE	219/011
CHLOROWAX 40	106/031
CHLOROWAX 40	163/009
CHLOROWAX 500C	106/032
CHLOROWAX 500C	163/010
CHLOROWAX 500C	212/038
CHLORPHENIRAMINE MALEATE	82/023
CHLORPHENIRAMINE MALEATE	87/031
CHLORPHENIRAMINE MALEATE	106/033
CHLORPROPAMIDE	87/032
CHROMIC ACID	220/005
CHROMITE SAND	P/125
CHROMIUM CARBONYL	70/093
CHROMIUM CARBONYL	87/033
CHROMIUM CARBONYL	218/001
C.I. ACID ORANGE 3	63/040
C.I. ACID ORANGE 3	106/034
C.I. ACID ORANGE 10	63/039
C.I. ACID ORANGE 10	P/131

CHEMICAL	PAGE/SEQ
C.I. ACID RED 14	87/034
C.I. ACID RED 114	P/138
C.I. ACID RED 114	P/139
C.I. ACID RED 114	78/006
C.I. ACID RED 114	106/035
C.I. ACID RED 114	117/004
C.I. ACID RED 114	140/011
C.I. ACID YELLOW 151	P/204
C.I. ACID YELLOW 151	215/004
C.I. ACID YELLOW 151	221/007
C.I. BASIC ORANGE 2	79/010
C.I. BASIC RED 9	85/020
C.I. BASIC RED 9	106/036
C.I. BASIC RED 9	164/012
C.I. BASIC RED 18	P/204
C.I. BASIC RED 18	216/005
C.I. BASIC RED 18	221/008
C.I. DIRECT BLACK 114	70/094
C.I. DIRECT BLACK 114	140/004
C.I. DIRECT BLUE 6	140/002
C.I. DIRECT BLUE 8	140/005
C.I. DIRECT BLUE 10	140/006
C.I. DIRECT BLUE 15	P/138
C.I. DIRECT BLUE 15	P/139
C.I. DIRECT BLUE 15	106/037
C.I. DIRECT BLUE 15	117/005
C.I. DIRECT BLUE 15	140/007
C.I. DIRECT BLUE 15	167/005
C.I. DIRECT BLUE 25	140/012
C.I. DIRECT BLUE 53	140/013
C.I. DIRECT BLUE 218	P/138
C.I. DIRECT BLUE 218	P/139
C.I. DIRECT BLUE 218	116/005
C.I. DIRECT BLUE 218	140/008
C.I. DIRECT BLUE 218	166/006
C.I. DIRECT ORANGE 6	70/095
C.I. DIRECT ORANGE 6	140/014
C.I. DIRECT RED 2	140/015
C.I. DIRECT RED 39	140/016
C.I. DIRECT RED 80	P/204
C.I. DIRECT RED 80	216/006
C.I. DIRECT RED 80	221/009
C.I. DIRECT VIOLET 32	140/009
C.I. DIRECT YELLOW 4	P/204
C.I. DIRECT YELLOW 4	216/007
C.I. DIRECT YELLOW 4	221/010
C.I. DIRECT YELLOW 11	P/44
C.I. DISPERSE BLUE 1	63/041
C.I. DISPERSE BLUE 1	106/038
C.I. DISPERSE BLUE 1	163/011
C.I. DISPERSE BLUE 1	164/013
C.I. DISPERSE BLUE 27	70/100
C.I. DISPERSE BROWN 1	P/204
C.I. DISPERSE BROWN 1	216/008
C.I. DISPERSE BROWN 1	221/011
C.I. DISPERSE YELLOW 3	P/131
C.I. PIGMENT BLUE 15	212/039
C.I. PIGMENT ORANGE 7	70/096
C.I. PIGMENT RED 2	70/097
C.I. PIGMENT RED 3	106/039
C.I. PIGMENT RED 3	117/006
C.I. PIGMENT RED 8	70/098
C.I. PIGMENT RED 23	106/040
C.I. PIGMENT RED 23	117/007
C.I. PIGMENT RED 69	70/099
C.I. SOLVENT YELLOW 14	63/042
C.I. SOLVENT YELLOW 14	P/131
1,8-CINEOL	104/006
1,8-CINEOLE	P/119
1,8-CINEOLE	P/122
CINNAMALDEHYDE	P/119
CINNAMALDEHYDE	P/122

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
CINNAMALDEHYDE	78/007
CINNAMALDEHYDE	104/007
CINNAMALDEHYDE	197/002
CINNAMALDEHYDE	198/007
CINNAMALDEHYDE ETHYLENE GLYCOL ACETAL	70/101
CINNAMYL ANTHRANILATE	64/043
CINNAMYL ANTHRANILATE	80/025
CINQUASIA RED	P/204
CINQUASIA RED	215/003
CINQUASIA RED	220/006
CITRAL	P/44
CITRAL	85/021
CITRAL	198/008
CLONITRALID	70/102
CLORAZEPATE	210/008
COAL DUST	P/183
COAL SLAGS	P/183
COAL TAR	P/126
COAL TAR PITCHES	P/151
COBALT	P/183
COBALT NAPHTHENATE	212/040
COBALTOCENE	70/103
COCONUT DIETHANOLAMIDE	64/044
COCONUT DIETHANOLAMIDE	82/024
COCONUT DIETHANOLAMIDE	107/041
CODEINE	64/045
CODEINE	104/008
CODEINE	232/001
CODEINE PHOSPHATE	64/046
CODEINE PHOSPHATE	85/022
COTTON MILL DUST	P/183
COUMAPHOS	70/104
COUMAPHOS	82/025
COUMAPHOS	87/035
COUMARIN	78/008
COUMARIN	107/042
M-CRESIDINE	70/105
P-CRESIDINE	70/106
O-CRESYL GLYCIDYL ETHER	70/107
CROTONALDEHYDE	P/144
CROTONALDEHYDE	114/010
CROTONALDEHYDE	114/011
CROTONALDEHYDE	198/009
4-CUMYLPHENYLDIPHENYL PHOSPHATE (CPDPP MIXED ISOMERS)	70/108
P-CUMYL PHENYL GLYCIDYL ETHER	70/109
1,2-CYCLOHEXANEDICARBOXYLIC ACID, BIS(OXIRANYLMETHYL) ESTER	70/110
CYCLOHEXANONE	80/026
CYCLOHEXANONE	118/002
CYCLOHEXANONE	163/012
CYCLOHEXIMIDE	70/111
CYCLOHEXYL ANTHRANILATE	64/047
CYCLOPHOSPHAMIDE	87/036
CYCLOSPORIN A	70/112
CYCLOSPORIN A	87/037
CYTARABINE	70/113
CYTEMBENA	70/114
DACARBAZINE	64/048
DAMMAR	64/049
D & C RED 9	64/050
D AND C RED 9	P/131
D AND C RED NO. 33	P/19
D AND C YELLOW NO. 11	P/204
D AND C YELLOW NO. 11	70/115
D AND C YELLOW NO. 11	216/009
D AND C YELLOW NO. 11	223/006
DDE	P/190
DDE	P/192
p,p'-DDT	P/177
p,p'-DDT	P/178
DDT AND METABOLITES	236/015

CHEMICAL	PAGE/SEQ
DECABROMODIPHENYL OXIDE	P/145
DECABROMODIPHENYL OXIDE	80/027
DECABROMODIPHENYL OXIDE	87/038
DECABROMODIPHENYL OXIDE	107/043
DECABROMODIPHENYL OXIDE	163/[illegible]13
DECALIN	197/003
DECANOIC ACID	70/116
M-DEET	P/151
DEHYDROEMETINE HYDROCHLORIDE	70/117
DIALLYLPHTHALATE	P/44
DIALLYL PHTHALATE	P/185
DIALLYL PHTHALATE	P/186
DIALLYL PHTHALATE	82/026
DIALLYLPHTHALATE	100/006
DIALLYL PHTHALATE	164/014
2,4-DIAMINOANISOLE SULFATE	70/118
DIAMINOMALEONITRILE	64/051
2,4-DIAMINOPHENOL DIHYDROCHLORIDE	80/028
2,4-DIAMINOPHENOL DIHYDROCHLORIDE	107/044
2,4-DIAMINOPHENOL DIHYDROCHLORIDE	117/008
2,4-DIAMINOPHENOL-DIHYDROCHLORIDE	167/006
4,4'-DIAMINO-2,2'-STILBENEDISULFONIC ACID	107/045
4,4'-DIAMINO-2,2'-STILBENEDISULFONIC ACID	117/009
3,4-DIAMINOTOLUENE	70/119
O-DIANISIDINE	140/003
DIARYLANILIDE YELLOW	87/039
DIAZEPAM	210/009
DIAZINON	P/131
DIAZINON	64/052
DIAZINON	82/027
DIAZINON	87/040
DIBENZOOXATHIANE	64/053
DIBROMOACETALDEHYDE	70/120
DIBROMOACETONITRILE	211/020
2,3-DIBROMO-2-BUTENE-1,4-DIOL	79/011
1,2-DIBROMO-3-CHLOROPROPANE	64/054
1,2-DIBROMO-3-CHLOROPROPANE	87/041
1,2-DIBROMO-3-CHLOROPROPANE	195/004
1,2-DIBROMO-3-CHLOROPROPANE	196/009
1,2-DIBROMO-3-CHLOROPROPANE	P/54
1,2-DIBROMO-3-CHLOROPROPANE	P/55
1,2-DIBROMO-3-CHLOROPROPANE	P/129
1,2-DIBROMO-4(1,2,-DIBROMOETHYL) CYCLOHEXANE	P/203
1,2-DIBROMO-4-(1,2-DIBROMOETHYL) CYCLOHEXANE	P/204
1,2-DIBROMO-4-(1,2-DIBROMOETHYL) CYCLOHEXANE	87/042
1,2-DIBROMOETHANE	P/124
DIBROMOMANNITOL	87/043
2,3-DIBROMO-1-PROPANOL	P/169
2,3-DIBROMO-1-PROPANOL	80/029
2,3-DIBROMO-1-PROPANOL	107/046
DI-SEC-BUTANOLAMINE	71/172
DI-TERT-BUTYL PEROXIDE	64/055
N,N'-DI-SEC-BUTYL-P-PHENYLDIAMINE	71/173
DIBUTYL PHENYL PHOSPHATE	70/121
DI-N-BUTYLPHTHALATE	196/016
DI(N-BUTYL) PHTHALATE	197/004
DI-N-BUTYLPHTHALATE	P/186
DIBUTYLTIN-BIS(LAURYLMERCAPTIDE)	64/056
DIBUTYLTIN DIACETATE	78/009
DIBUTYLTIN DIACETATE	82/028
DIBUTYLTIN DIACETATE	87/044
DIBUTYLTIN DILAURATE	64/057
DICHLORAN	70/122
DICHLORAN	78/010
DICHLORETHANE	P/127
DICHLOROACETALDEHYDE	70/123
DICHLOROACETONITRILE	87/045

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
DICHLOROACETONITRILE	211/021
3,4-DICHLOROANILINE	64/058
1,2-DICHLOROBENZENE	164/015
1,4-DICHLOROBENZENE	P/135
p-DICHLOROBENZENE	163/014
p-DICHLOROBENZENE	164/016
1,2-DICHLOROBENZENE (O-DICHLOROBENZENE)	82/030
1,4-DICHLOROBENZENE (P-DICHLOROBENZENE)	82/029
1,4-DICHLOROBENZENE (P-DICHLOROBENZENE)	107/047
5,6-DICHLORO-2-BENZOTHIAZOLAMINE	70/124
5,6-DICHLORO-2-BENZOTHIAZOLAMINE	223/007
1,3-DICHLORO-5,5-DIMETHYLHYDANTION	197/005
1,3-DICHLORO-5,5-DIMETHYLHYDANTOIN	P/144
DICHLORODIPHENYLETHYLENE	82/031
1,2-DICHLOROETHANE	P/124
1,2-DICHLOROETHANE	64/059
CIS-1,2-DICHLOROETHYLENE	70/125
DICHLOROMETHANE (METHYLENE CHLORIDE)	82/032
DICHLOROMETHANE (METHYLENE CHLORIDE)	107/048
DICHLOROMETHANE (METHYLENE CHLORIDE)	164/017
4,5-DICHLORO-6-METHYL-2-METHYLSULFONYLPYRIMIDINE	70/126
3,4-DICHLORONITROBENZENE	87/046
2,4-DICHLORONITROBENZENE	88/047
2,3-DICHLORONITROBENZENE	88/048
2,4-DICHLOROPHENOL	80/030
2,4-DICHLOROPHENOL	107/049
1,2-DICHLOROPROPANE	P/44
2,3-DICHLORO-1-PROPANOL	64/060
1,3-DICHLORO-2-PROPANOL	70/127
1,3-DICHLOROPROPENE	P/44
1,3-DICHLOROPROPENE (TELONE II)	88/049
1,3-DICHLOROPROPENE (TELONE II)	164/018
2,3-DICHLOROPROPENE	P/148
2,3-DICHLOROPROPYLENE	70/128
2,3-DICHLOROPROPYLENE	221/012
DICHLORVOS	P/48
DICHLORVOS	70/129
DICHLORVOS	80/031
DICHLORVOS	85/023
DICHLORVOS	107/050
DICUMYL PEROXIDE	64/061
DICYCLOHEXYLAMINE NITRITE	64/062
DICYCLOHEXYLPHOSPHINE	212/028
N,N'-DICYCLOHEXYLTHIOUREA	64/063
N,N'-DICYCLOHEXYLTHIOUREA	80/032
N,N'-DICYCLOHEXYLTHIOUREA	82/033
N,N'-DICYCLOHEXYLTHIOUREA	85/024
DIELDRIN	88/050
1,2:3,4-DIEPOXYBUTANE DL	80/033
DIESEL EXHAUST	P/183
DIESEL FUEL MARINE	107/051
DIESEL FUEL MARINE	163/015
DIETHANOLAMINE	82/034
DIETHANOLAMINE	88/051
DIETHANOLAMINE	107/052
DIETHANOLAMINE	198/010
5-DIETHYLAMINO-2-NITROSO-4-METHYLPHENOL	70/130
5-DIETHYLAMINO-2-NITROSOPHENOL HCL	70/131
3-DIETHYLAMINOPHENOL	70/132
DIETHYLBUTYLAMINE	64/064
N,N'-DIETHYLCARBANILIDE	70/133
DIETHYLDICHLOROSILANE	70/134
DIETHYLENE GLYCOL	196/026
DIETHYLENE GLYCOL BIS-GLYCIDYL ETHER	70/135
DIETHYLENE GLYCOL DIMETHYL ETHER	194/009
DIETHYLENE GLYCOL DIMETHYL ETHER	232/002
DIETHYLENE GLYCOL MONOETHYL ETHER	196/027
DIETHYLENE GLYCOL MONOETHYL ETHER	P/170
DIETHYLENE GLYCOL MONOETHYL ETHER	P/190
DIETHYLENE GLYCOL MONOMETHYL ETHER	P/190
DI(2-ETHYLHEXYL)ADIPATE	P/186
DI(2-ETHYLHEXYL)ADIPATE	78/011
DI(2-ETHYLHEXYL)ADIPATE	82/035
2,2'-DIETHYLHEXYLAMINE	70/136
DI(2-ETHYLHEXYL) PHTHALATE	P/56
DI(2-ETHYLHEXYL) PHTHALATE	P/185
DI(2-ETHYLHEXYL)PHTHALATE	P/186
DI(2-ETHYLHEXYL) PHTHALATE	80/034
DI(2-ETHYLHEXYL) PHTHALATE	85/025
DI(2-ETHYLHEXYL)PHTHALATE	164/019
DI(2-ETHYLHEXYL)PHTHALATE	195/005
DI-2-ETHYLHEXYL PHTHALATE	196/018
DI(2-ETHYLHEXYL) PHTHALATE	197/007
DI(2-ETHYLHEXYL)PHTHALATE	235/002
DI-(2-ETHYLHEXYL)SEBACTE (DEHS)	213/041
DIETHYLNITROSAMINE	P/159
N,N-DIETHYL-4-((5-NITRO-2-THIAZOLYL) AZO) BENZENAMINE	70/137
N,N-DIETHYL-P-PHENYLENEDIAMINE	70/138
DIETHYL PHTHALATE	P/186
DIETHYL PHTHALATE	104/009
DIETHYL PHTHALATE	116/007
DIETHYL PHTHALATE	197/006
DI-N-ETHYL PHTHALATE	196/017
DIETHYLSTILBESTROL	P/56
DIETHYLSTILBESTROL	80/035
DIETHYLSTILBESTROL	85/026
DIETHYLSTILBESTROL	195/006
DIETHYLSTILBESTROL	195/007
DIETHYLSTILBESTROL	196/002
DIETHYLSTILBESTROL	235/003
DIETHYLSTILBESTROL DERIVATIVES	235/004
N,N'-DIETHYLTHIOUREA	82/036
N,N-DIETHYL-M-TOLUAMIDE	P/170
N,N-DIETHYL-M-TOLUAMIDE	P/191
N,N-DIETHYL-M-TOLUAMIDE	232/003
2,4-DIFLUOROANILINE	64/065
DIGITONIN	71/139
DIGLYCIDYL RESORCINOL ETHER	82/037
DIGLYCIDYL RESORCINOL ETHER	85/027
DIHEXYLAMINE	64/066
DI-N-HEXYLPHTHALATE	P/186
DI-N-HEXYL PHTHALATE	196/019
DI(N-HEXYL) PHTHALATE	197/008
DI(N-HEXYL)PHTHALATE	233/004
3,4-DIHYDROCOUMARIN	116/006
1,2-DIHYDRO-2,2,2-TRIMETHYLQUINOLINE	P/149
1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE (MONOMER)	85/028
1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE (MO	114/012
1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE (PO	114/013
3,3'-DIHYDROXYBENZIDINE	71/140
1,8-DIHYDROXY-4,5-DINITROANTHRAQUINONE	78/012
1,8-DIHYDROXY-4,5-DINITROANTHRAQUINONE	88/052
DIHYDROXYUREA	71/141
DI(ISO-BUTYL) PHTHALATE	197/009
DIISOBUTYLPHTHALATE	P/186
2,6-DIISOCYANATOTOLUENE	64/067
DIISODECYL PHTHALATE	P/186
DI(ISO-DECYL) PHTHALATE	197/010
DI(ISOPROPYLPHENYL)PHENYL PHOSPHATE (DIPP)	71/142
2,5-DIKETOPIPERAZINE	213/042
DIMETHOXANE	85/029
DIMETHOXANE	107/053
DIMETHOXANE	167/007
2,4-DIMETHOXYANILINE HYDROCHLORIDE	71/143

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
2,4-DIMETHOXYANILINE HYDROCHLORIDE	82/038
2,4-DIMETHOXYANILINE HYDROCHLORIDE	88/053
DIMETHOXYBENZIDINE	P/139
DIMETHOXYBENZIDINE	P/230
3,3'-DIMETHOXYBENZIDINE	P/23
3,3'-DIMETHOXYBENZIDINE	P/138
3,3'-DIMETHOXYBENZIDINE	107/054
3,3'-DIMETHOXYBENZIDINE	117/010
3,3'-DIMETHOXYBENZIDINE	167/008
3,3'-DIMETHOXYBENZIDINE-4, 4'-DIISOCYANATE	P/131
4,4'-DIMETHOXYDIPHENYLAMINE	71/144
N,N-DIMETHYLACETAMIDE	P/170
4-DIMETHYLAMINOAZOBENZENE	71/145
3-DIMETHYLAMINO-4-METHYLPHENOL	71/146
5-DIMETHYLAMINO-2-NITROSO-4-METHYLPHENOL	71/147
3-DIMETHYLAMINOPHENOL	64/068
N,N-DIMETHYLANILINE	80/036
N,N-DIMETHYLANILINE	88/054
N,N-DIMETHYLANILINE	107/055
7,12-DIMETHYLBENZ(A)ANTHRACENE	78/013
DIMETHYLBENZIDINE	P/139
DIMETHYLBENZIDINE	P/230
3,3'-DIMETHYLBENZIDINE	P/23
3,3'-DIMETHYLBENZIDINE	P/138
3,3'-DIMETHYLBENZIDINE	107/056
3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE	71/148
2,5-DIMETHYL-2,5-BIS(TERT-BUTYLPEROXY) HEXANE	64/069
TRANS-1,3-DIMETHYLCYCLOPENTANE	71/149
DIMETHYLETHANOLAMINE	79/012
DIMETHYLFORMAMIDE	P/124
DIMETHYLFORMAMIDE	P/127
DIMETHYLFORMAMIDE	80/037
DIMETHYLFORMAMIDE	88/055
DIMETHYL HYDROGEN PHOSPHITE	80/038
DIMETHYL HYDROGEN PHOSPHITE	85/030
DIMETHYL HYDROGEN PHOSPHITE	100/007
DIMETHYLHYDROGEN PHOSPHITE	164/020
1,1-DIMETHYL-1-(2-HYDROXPROPYLAMINE) METHACRYLIMIDE	64/070
1,1-DIMETHYL-1-(2-HYDROXYPROPYL-AMINE)TETRADECANIMIDE	71/150
DIMETHYL METHYLPHOSPHONATE	79/013
DIMETHYL METHYLPHOSPHONATE	80/039
DIMETHYL METHYLPHOSPHONATE	107/057
DIMETHYL METHYL PHOSPHONATE	163/016
DIMETHYL METHYLPHOSPHONATE	197/011
DIMETHYL MORPHOLINOPHOSPHORAMIDATE	79/014
DIMETHYL MORPHOLINOPHOSPHORAMIDATE	80/040
DIMETHYL MORPHOLINOPHOSPHORAMIDATE	85/031
DIMETHYL MORPHOLINOPHOSPHORAMIDATE	107/058
DIMETHYL MORPHOLINOPHOSPHORAMIDATE (DMMPA)	164/021
1,2-DIMETHYL-3-NITROBENZENE	71/151
1,2-DIMETHYL-4-NITROBENZENE	71/152
1,3-DIMETHYL-2-NITROBENZENE	71/153
1,3-DIMETHYL-4-NITROBENZENE	71/154
1,3-DIMETHYL-5-NITROBENZENE	71/155
1,4-DIMETHYL-2-NITROBENZENE	71/156
DIMETHYLNITROSAMINE	P/190
DIMETHYLNITROSAMINE	P/192
DIMETHYLOLDIHYDROXYETHYLENEUREA	79/015
DIMETHYLOLDIHYDROXYETHYLENEUREA	104/010
DIMETHYLOLDIHYDROXYETHYLENUREA	166/007
N,N-DIMETHYL-P-PHENYLENEDIAMINE	71/157
DIMETHYL PHTHALATE	P/186
DIMETHYL PHTHALATE	116/011
DIMETHYL PHTHALATE	235/005
DIMETHYL SULFOXIDE	71/158
DIMETHYL TEREPHTHALATE	88/056

CHEMICAL	PAGE/SEQ
DIMETHYLVINYL CHLORIDE	79/016
DIMETHYLVINYL CHLORIDE	80/041
DIMETHYLVINYL CHLORIDE	85/032
DIMETHYLVINYL CHLORIDE	107/059
DIMETHYLVINYL CHLORIDE	107/060
DIMETHYLVINYL CHLORIDE (DMVC)	164/022
DIMETHYLVINYLCHLORIDE	176/002
N,N'-DI-2-NAPTHYL-P-PHENYLENEDIAMINE	71/159
2,4-DINITROANILINE	P/150
2,4-DINITROANILINE	71/160
2,4-DINITROANILINE	78/014
2,4-DINITROANILINE	88/057
2-(2,4-DINITROANILINO)PHENOL	71/161
4-(2,4-DINITROANILINO)PHENOL	64/071
2,5-DINITRO-9H-FLUORENE	71/162
2,7-DINITRO-9H-FLUOREN-9-ONE	71/163
2,7-DINITRO-9H-FLUOREN-9-ONE	85/033
2,7-DINITRO-9H-FLUOREN-9-ONE	88/058
2,4-DINITRO-6-(1-METHYLHEPTYL) PHENOL	71/164
1,3-DINITRONAPHTHALENE	71/165
1,8-DINITRONAPHTHALENE	71/166
1,5-DINITRONAPHTHALENE	71/167
1,5-DINITRONAPHTHALENE	85/034
2,4-DINITROPHENOL	71/168
1,3-DINITROPYRENE	P/204
1,6-DINITROPYRENE	P/204
1,8-DINITROPYRENE	P/204
2,4-DINITROTOLUENE	88/059
4,4'-DIOCTYLDIPHENYLAMINE	71/169
DI-N-OCTYLPHTHALATE	196/020
DI(N-OCTYL) PHTHALATE	197/012
DI(N-OCTYL)TIN-S,S'-BIS(ISOOCTYL-MERCAPTOACETATE)	64/072
DI(N-OCTYL)TIN MALEATE	64/073
1,4-DIOXANE	82/039
DIOXATHION	85/035
DI-N-PENTYL PHTHALATE	196/021
DIPHENHYDRAMINE HYDROCHLORIDE	82/040
DIPHENHYDRAMINE HYDROCHLORIDE	88/060
DIPHENHYDRAMINE HYDROCHLORIDE	108/061
DIPHENYLHYDANTOIN	P/96
DIPHENYLHYDANTOIN	P/172
5,5-DIPHENYLDANTOIN	P/178
N,N'-DIPHENYL-P-PHENYLENEDIAMINE	71/170
ASYM-DIPHENYLUREA	71/171
DI-N-PROPYLPHTHALATE	196/022
DIRECT BLACK 38	P/92
DIRECT BLUE 15	P/92
DIRECT RED 2	P/92
DIRECT VIOLET 32	64/075
DISPERSE YELLOW 3	P/31
DISPERSE YELLOW 3	P/125
DISPERSE YELLOW 3	P/127
DISULFIRAM	P/124
DISULFIRAM	197/013
DMBA/TPA/BPO (7,12-DIMETHYLBENZ(A)ANTH	116/008
DMBA/TPA/BPO (7,12-DIMETHYLBENZ(A)ANTH	116/009
DMBA/TPA/BPO (7,12-DIMETHYLBENZ(A)ANTH	116/010
DOXYLAMINE	P/119
DOXYLAMINE	P/120
DOXYLAMINE	P/122
DOXYLAMINE	108/062
DOXYLAMINE	166/008
ECONAZOLE	71/174
ENDRIN	82/041
ENDRIN	88/061
EPHEDRINE SULFATE	64/076
EPHEDRINE SULFATE	82/042
EPHEDRINE SULFATE	85/036
EPHEDRINE SULFATE	108/063
EPHEDRINE SULFATE	163/017

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
EPIBROMOHYDRIN	79/017
EPINEPHRINE	64/077
EPINEPHRINE HYDROCHLORIDE	108/064
EPINEPHRINE HYDROCHLORIDE	167/009
2,3-EPOXYBUTANE	71/175
1,2-EPOXYBUTANE	80/042
1,2-EPOXYBUTANE	82/043
1,2-EPOXYBUTANE	85/037
1,2-EPOXYBUTANE	108/065
1,2-EPOXY-3-BUTENE	71/176
1,2-EPOXYDECANE	71/177
2,3-EPOXY-1,4-DICHLOROBUTANE	71/178
2,3-EPOXY-2,3-DIMETHYLBUTANE	71/179
1,2-EPOXYDODECANE	71/180
1,2-EPOXY-3-FLUOROPROPANE	71/181
1,2-EPOXYHEXADECANE	82/044
1,2-EPOXYHEXADECANE	88/062
1,2-EPOXYHEXADECANE	108/066
1,2-EPOXY-1,1,2,3,3,3-HEXAFLUOROPROPANE	71/182
1,2-EPOXYOCTADECANE	71/183
9,10-EPOXYOCTADECANOIC ACID, 2-ETHYLHEXYL ESTER	71/184
1,2-EPOXYTETRADECANE	72/185
1,2-EPOXY-3,3,3-TRICHLOROPROPANE	78/015
1,2-EPOXY-3,3,3-TRICHLOROPROPANE	88/063
ERYTHROMYCIN STEARATE	81/043
ERYTHROMYCIN STEARATE	88/064
ERYTHROMYCIN STEARATE	108/067
ESTROGENS	P/172
ETHACRYNIC ACID	64/078
ETHANOL	P/56
ETHANOL	P/180
ETHANOL	P/190
ETHANOL	196/028
ETHANOL	233/005
ETHANOLAMINE	198/011
ETHINYLESTRADIOL	72/186
ETHIONAMIDE	64/079
ETHIONAMIDE	72/187
2-ETHOXY ACETIC ACID	196/029
2-ETHOXY ETHANETHIOL	197/014
2-ETHOXYETHANOL	P/151
2-ETHOXYETHANOL (EGMEE)	82/045
2-ETHOXYETHANOL (EGMEE)	108/068
2-ETHOXYETHANOL	211/015
2-ETHOXYETHANOL ACETATE	211/016
N-(3-ETHOXYPHENYL)ACETAMIDE	72/188
3-ETHOXY-1-PROPANOL	197/015
3-ETHOXY-1-PROPANOL	198/012
ETHYL ACETATE	72/189
ETHYL ACRYLATE	64/080
ETHYLAMINE	P/137
3-ETHYLAMINO-4-METHYLPHENOL	64/081
3-ETHYLAMINOPHENOL	64/082
ETHYLBENZENE	P/134
ETHYL BENZENE	P/151
ETHYL BENZENE	P/170
ETHYLBENZENE	64/083
ETHYLBENZENE	85/038
ETHYL BROMIDE	88/065
ETHYL BROMIDE	108/069
ETHYL CHLORIDE	72/190
ETHYL CHLORIDE	108/070
S-(ETHYL)CHLOROTHIOFORMATE	P/203
S-(ETHYL)CHLOROTHIOFORMIC ACID	72/191
1-ETHYL-4-(DIETHYLDIAMINE)PIPERAZINE	72/192
N-ETHYL-N,N-DIPHENYLUREA	72/193
S-ETHYL DIPROPYLTHIOCARBAMATE	72/194
S-ETHYL DIPROPYLTHIOCARBAMATE	78/016
ETHYLENEDIAMINE	65/084
ETHYLENEDIAMINE TETRAACETIC ACID (EDTA)	65/085

CHEMICAL	PAGE/SEQ
ETHYLENEDIAMINE TETRAACETIC ACID (EDTA)	82/046
ETHYLENEDIAMINE TETRAACETIC ACID (EDTA)	88/066
ETHYLENE DIBROMIDE	P/23
ETHYLENE DIBROMIDE	P/50
ETHYLENE DIBROMIDE	P/54
ETHYLENE DIBROMIDE	P/55
ETHYLENE DIBROMIDE	P/173
ETHYLENE DIBROMIDE	P/191
ETHYLENE DIBROMIDE	P/193
ETHYLENE DIBROMIDE	164/023
ETHYLENE DIBROMIDE	234/003
ETHYLENE GLYCOL	P/188
ETHYLENE GLYCOL	81/044
ETHYLENE GLYCOL	88/067
ETHYLENE GLYCOL	108/071
ETHYLENE GLYCOL	117/011
ETHYLENE GLYCOL	194/004
ETHYLENE GLYCOL	195/008
ETHYLENE GLYCOL	196/003
ETHYLENE GLYCOL	196/030
ETHYLENE GLYCOL	232/004
ETHYLENE GLYCOL	233/006
ETHYLENE GLYCOL (POSTNATAL STUDY)	194/010
ETHYLENE GLYCOL MONOBUTYL ETHER	196/031
ETHYLENE GLYCOL MONOBUTYL ETHER	233/007
ETHYLENE GLYCOL MONOBUTYL ETHER	P/170
ETHYLENE GLYCOL MONOBUTYL ETHER	P/190
ETHYLENE GLYCOL MONOETHYL ETHER	P/170
ETHYLENE GLYCOL MONOETHYL ETHER	P/190
ETHYLENE GLYCOL MONOETHYL ETHER	P/191
ETHYLENE GLYCOL MONOETHYL ETHER	163/018
ETHYLENE GLYCOL MONOETHYL ETHER	164/024
ETHYLENE GLYCOL MONOETHYL ETHER	195/009
ETHYLENE GLYCOL MONOETHYL ETHER	196/032
ETHYLENE GLYCOL MONOETHYL ETHER ACETATE	196/033
ETHYLENE GLYCOL MONOETHYL ETHER ACETATE	P/190
ETHYLENE GLYCOL MONOMETHYL ETHER	P/189
ETHYLENE GLYCOL MONOMETHYL ETHER	P/191
ETHYLENE GLYCOL MONOMETHYL ETHER	P/192
ETHYLENE GLYCOL MONOMETHYL ETHER	196/034
ETHYLENE GLYCOL MONOMETHYL ETHER ACETATE	P/170
ETHYLENE GLYCOL MONOPHENYL ETHER	196/035
ETHYLENE OXIDE	P/50
ETHYLENE OXIDE	P/55
ETHYLENE OXIDE	72/195
ETHYLENE OXIDE	88/068
ETHYLENE OXIDE	108/072
N-ETHYLENE-TETRAETHYLPENTAMINE	72/196
ETHYLENE THIOUREA	78/017
ETHYLENE THIOUREA	83/047
ETHYLENE THIOUREA	108/073
ETHYLENE THIOUREA	117/012
ETHYLENETHIOUREA	P/96
2-ETHYLHEXANAL	72/197
2-ETHYLHEXANOIC ACID	65/086
2-ETHYLHEXANOIC ACID	88/069
2-ETHYLHEXANOL	P/186
2-ETHYLHEXANOL	88/070
2-ETHYLHEXANOL	223/008
2-ETHYL-1-HEXANOL	197/016
2-ETHYLHEXENAL	72/199
2-ETHYL-2-HEXENAL	72/198
2-ETHYLHEXYL ACID SULFATE	P/186
2-ETHYLHEXYL ACRYLATE	65/087
2-ETHYLHEXYLAMINE	72/200
2-ETHYLHEXYL GLYCIDYL ETHER	72/201

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
3-((ETHYLHEXYL)OXY)PROPIONITRILE	72/202
3-((ETHYLHEXYL)OXY)PROPYLAMINE	72/203
ETHYLHYDROXY HEXANOIC ACID	72/204
ETHYL METHANESULFONATE	P/48
ETHYL METHANESULFONATE	P/51
ETHYL METHANESULFONATE	P/57
N-ETHYLMORPHOLINE	65/088
N-ETHYL-4-NITROANILINE	72/205
ETHYL NITROSOUREA	P/51
N-ETHYL-N-NITROSOUREA	P/53
N-ETHYL-N-NITROSOUREA	P/54
N-ETHYL-N-PHENYL BENZYLAMINE	65/089
ETHYL SILICATE	P/170
2-ETHYLTHIO ETHANETHIOL	197/017
2-ETHYLTHIO ETHANOL	197/018
N-ETHYL-O-TOLUENESULFONAMIDE	72/206
EUGENOL	79/018
EUGENOL	P/44
FD AND C RED NO. 3	P/19
FD AND C RED NO. 32	72/207
FD & C YELLOW NO. 6	72/208
FENDILINE	72/209
FERRIC AMMONIUM FERROCYANIDE	72/210
FERRIC AMMONIUM FERROCYANIDE	88/071
FERRIC AMMONIUM FERROCYANIDE	218/002
FERRIC CHLORIDE	83/049
FERRIC OXIDE	P/125
FERROCENE	218/003
FLUOMETURON	65/091
FLUOMETURON	83/050
FLUORESCEIN	P/44
FORMALDEHYDE	65/092
FORMALDEHYDE	78/018
FORMALDEHYDE	198/013
FORMANILIDE	65/093
FORMANILIDE	72/211
FORMIC ACID	221/013
FORMULATED FENAMINOSULF	65/090
FUMARIC ACID	65/094
FURAN	P/124
FURAN	79/019
FURAN	83/051
FURAN	88/072
FURAN	108/074
FURAN	167/010
FURAN	167/011
FURAN	167/012
FURAN	213/043
FURFURAL	81/045
FURFURAL	108/075
FURFURAL	198/014
FURFURYL ALCOHOL	213/044
FUROSEMIDE	83/052
FUROSEMIDE	108/076
BETA-2-FURYLACROLEIN	65/095
GALLIUM ARSENIDE	P/204
GALLIUM ARSENIDE	219/013
GALLIUM ARSENIDE	223/009
GENTIAN VIOLET	P/33
GENTIAN VIOLET	P/119
GENTIAN VIOLET	P/121
GENTIAN VIOLET	P/122
GENTIAN VIOLET	P/152
GENTIAN VIOLET	P/153
GENTIAN VIOLET	108/077
GLUTARALDEHYDE	78/019
GLUTARALDEHYDE	81/046
GLUTARALDEHYDE	108/078
GLUTARALDEHYDE	164/025
GLUTARALDEHYDE	198/015
GLYCIDOL	65/096
GLYCIDOL	79/020
GLYCIDOL	81/047
GLYCIDOL	85/040
GLYCIDOL	108/079
GLYCIDYL ACRYLATE	72/212
GLYCIDYL METHACRYLATE	72/213
GLYCOL (POLYSORBATE 80)	108/080
GRISEOFULVIN	72/214
HALOTHANE	78/020
HAMAMELIS WATER (WITCH HAZEL)	81/048
HAMAMELIS WATER (WITCH HAZEL)	165/001
HAMAMELIS WATER (WITCH HAZEL WATER)	100/008
HC BLUE 1	P/44
HC BLUE 1	81/049
HC BLUE 1	101/009
HC BLUE 1	165/002
HC BLUE 2	P/44
HC BLUE 2	65/097
HC BLUE 2	83/053
HC BLUE 2	101/010
HC BLUE 2	165/003
HC RED 3	65/098
HC RED 3	109/081
HC RED 3	165/004
HC YELLOW 4	78/021
HC YELLOW 4	88/073
HC YELLOW 4	109/082
HC YELLOW 4	117/013
HC YELLOW 4	167/013
HEPTACHLOR	83/054
HEPTACHLOR	85/041
1,2,3,4,6,7-HEXABROMONAPHTHALENE	72/215
HEXABROMONAPHTHALENES	P/147
1,2,3,4,6,7-HEXABROMONAPTHALENE	P/147
2,3,4,5,6,7-HEXABROMONAPTHALENE	P/147
HEXACHLOROBENZENE	88/074
2,3,4,5,3',4'-HEXACHLOROBIPHENYL	P/148
2,3,6,2',3',6'-HEXACHLOROBIPHENYL	P/146
2,4,5,2',4',5'-HEXACHLOROBIPHENYL	P/146
2,4,5,2',4',5'-HEXACHLOROBIPHENYL	P/148
HEXACHLORO-1,3-BUTADIENE	P/130
HEXACHLORO-1,3-BUTADIENE	P/143
HEXACHLORO-1,3-BUTADIENE	114/014
1,2,3,4,5,6-HEXACHLOROCYCLOHEXANE	P/177
HEXACHLOROCYCLOPENTADIENE	88/075
HEXACHLOROCYCLOPENTADIENE	104/011
1,2,3,6,7,8-HEXACHLORODIBENZO-P-DIOXIN	72/216
1,2,3,7,8,9-HEXACHLORODIBENZO-P-DIOXIN	234/004
HEXACHLOROETHANE	83/055
HEXACHLOROETHANE	109/083
HEXACHLORONAPHTHALENE	72/217
12-O-HEXADECANOYL-16-HYDROXYPHORBOL-13-ACETATE	213/045
HEXAFLUOROACETONE SESQUIHYDRATE	65/099
1,1,1,3,3,3-HEXAFLUORO-2-PROPANOL	72/218
1,6-HEXAMETHYLENE DIACRYLATE	65/100
HEXAMETHYLPHOSPHORAMIDE	P/54
HEXAMETHYLPHOSPHORAMIDE	P/56
HEXAMETHYL-P-ROSANILINE CHLORIDE	78/022
HEXAMETHYL-P-ROSANILINE CHLORIDE	109/084
HEXANAMIDE	85/042
HEXANE	P/151
N-HEXANE	P/180
1,6-HEXANEDIAMINE	114/015
1,3,6-HEXANETRICARBONITRILE	72/219
1-HEXANOL	P/181
HEXYL GLYCIDYL ETHER	72/220
HEXYLRESORCINOL	81/050
HEXYLRESORCINOL	109/085
HYCANTHONE METHANESULFONATE	72/221
4-(HYDOXYPHENYL)RETINAMIDE	213/046

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
HYDROCHLOROTHIAZIDE	81/051
HYDROCHLOROTHIAZIDE	109/086
HYDROCHLOROTHIAZIDE	167/014
HYDROCHLOROTHIAZIDE	194/005
HYDROCYANIC ACID	72/222
HYDROGEN SULFIDE	P/137
HYDROQUINONE	79/021
HYDROQUINONE	81/052
HYDROQUINONE	109/087
4-HYDROXYACETANILIDE	167/015
4-HYDROXYACETANILIDE	196/010
HYDROXYACETONITRILE	65/101
N-HYDROXYBENZAMIDE	65/102
ALPHA-HYDROXYBENZENEACETONITRILE	65/103
N-(HYDROXYETHYL)ETHYLENEDIAMINE	79/022
HYDROXYLAMINE, HYDROCHLORIDE	72/223
2-HYDROXY-4-METHOXYBENZOPHENONE	114/016
2-HYDROXY-4-METHOXYBENZOPHENONE	114/017
2-HYDROXY-2-METHYLPROPANENITRILE	65/104
2-HYDROXY-1,4-NAPHTHOQUINONE	79/023
3-HYDROXY-N-PHENYLANILINE	65/105
2-HYDROXYPROPANENITRILE	65/106
8-HYDROXYQUINOLINE	P/44
8-HYDROXYQUINOLINE	81/053
8-HYDROXYQUINOLINE	101/011
8-HYDROXYQUINOLINE	163/019
8-HYDROXYQUINOLINE	165/005
8-HYDROXYQUINOLINE SULFATE	72/224
IODINATED GLYCEROL	65/107
IODINATED GLYCEROL	81/054
IODINATED GLYCEROL	109/088
IODOACETIC ACID	72/225
IODOCHLOROHYDROXYQUINOLINE	72/226
IODOFORM	86/043
IRON DEXTRAN	83/056
ISATIN-5-SULFONIC ACID SODIUM SALT	79/024
ISOBUTYL ALCOHOL	72/227
ISOBUTYL NITRITE	166/009
ISOBUTYRALDEHYDE	83/057
ISOBUTYRALDEHYDE	86/044
ISOBUTYRALDEHYDE	166/010
ISODECYL METHACRYLATE	72/228
ISOPENTANE	213/047
ISOPHORONE	81/055
ISOPHORONE	86/045
ISOPHORONE	109/089
ISOPHORONE	165/006
ISOPHTHALIC DIGLYCIDYL ESTER	72/229
ISOPRENE	79/025
ISOPRENE	88/076
ISOPRENE	114/018
ISOPRENE (2-METHYL-1,3-BUTADIENE	P/134
ISOPROPANOL	P/180
ISO-PROPANOL	P/190
P-ISOPROPOXYDIPHENYLAMINE	72/230
N-ISOPROPYLANILINE	65/108
ISOPROPYL GLYCIDYL ETHER	79/027
N-ISOPROPYL-N'-PHENYL-P-PHENYLENEDIAMINE	197/019
ISOPROPYL PHENYL DIPHENYL PHOSPHATE (IPDP MIXED ISOMERS)	65/109
ISOPROTERENOL	P/137
KAEMPFEROL	213/048
LANTHANUM NITRATE HEXAHYDRATE	73/231
LASIOCARPINE	P/131
LASIOCARPINE	88/077
LAURIC ACID	73/232
LAURIC ACID DIETHANOLAMINE CONDENSATE	65/110
LAURIC ACID DIETHANOLAMINE CONDENSATE	83/058
LAURIC ACID DIETHANOLAMINE CONDENSATE	109/090
LAURYL GLYCIDYL ETHER	73/233
LEAD ACETATE	195/010
LEAD ACETATE	196/004
LEAD OXIDE	P/137
LEAD SULFIDE	P/137
LEUCO VAT BLUE 1	73/234
D-LIMONENE	83/059
D-LIMONENE	88/078
D-LIMONENE	109/091
LINDANE	P/178
LINOLELAIDIC ACID	221/014
LITHOCHOLIC ACID	73/235
LITHOCHOLIC ACID	86/046
LUMINOL	73/236
LUMINOL	216/010
LUMINOL	221/015
MACHINE OILS	P/126
MACHINE OILS	P/127
MALAOXON	73/237
MALATHION	83/060
MALATHION	217/011
MALONALDEHYDE	P/44
MALONALDEHYDE	109/092
MALONALDEHYDE	163/020
MALONALDEHYDE	165/007
MALONALDEHYDE	198/016
MALONALDEHYDE, SODIUM SALT	81/056
MALONALDEHYDE, SODIUM SALT	88/079
MALONIC DINITRILE	65/111
MALTOL	79/028
MANGANESE SULFATE	P/44
MANGANESE SULFATE	109/093
D-MANNITOL	83/061
MELAMINE	83/062
P-MENTHANE	65/112
PARA-MENTHANE HYDROPEROXIDE	65/113
DL-MENTHOL	65/114
DL-MENTHOL	73/238
2-MERCAPTOBENZIMIDAZOLE	P/144
2-MERCAPTOBENZIMIDAZOLE	65/115
2-MERCAPTOBENZIMIDAZOLE	83/063
2-MERCAPTOBENZIMIDAZOLE	88/080
MERCAPTOBENZOTHIAZOLE	83/064
MERCAPTOBENZOTHIAZOLE	86/047
MERCAPTOBENZOTHIAZOLE	109/094
2-MERCAPTO-4-METHYL-5-THIAZOLYL METHYL KETONE	73/239
6-MERCAPTOPURINE	P/54
MERCURIC CHLORIDE	P/132
MERCURIC CHLORIDE	P/133
MERCURIC CHLORIDE	79/029
MERCURIC CHLORIDE	83/065
MERCURIC CHLORIDE	86/048
MERCURIC CHLORIDE	109/095
MERCURIC CHLORIDE	117/014
MERCURY	P/151
METASYSTOX R	65/116
METHACRYLONITRILE	65/117
METHACRYLONITRILE	79/030
METHANOL	P/180
METHANOL	P/190
METHAPYRILENE	P/119
METHAPYRILENE	104/012
METHAPYRILENE	116/012
METHAPYRILENE	118/003
METHAPYRILENE HYDROCHLORIDE	83/066
METHAPYRILENE HYDROCHLORIDE	86/049
METHDILAZINE	166/011
METHOXYACETIC ACID	233/008
2-METHOXY ACETIC ACID	196/036
4-METHOXYBENZILIDINE-4'-N-BUTYLANILINE (MBBA)	73/240

ALPHABETIC INDEX TO TABLES

CHEMICAL PAGE/SEQ

6-METHOXY-2-BENZO-THIAZOLAMINE 223/010
3-((METHOXYCARBONYL)AMINO)PHENYL N-(3-METHYLPHENYL) CARBAMATE 73/241
METHOXYCHLOR 65/118
METHOXYCHLOR 86/050
2-METHOXYETHANOL P/151
2-METHOXYETHANOL 211/017
2-METHOXYETHANOL 233/009
2-METHOXYETHANOL ACETATE 211/018
2-METHOXYETHYL ACETATE 197/020
2-METHOXYETHYL ACRYLATE 197/021
METHOXYETHYL MERCURY CHLORIDE 73/242
METHOXYFLURANE 73/243
4-METHOXY-3-NITRO-N-PHENYLBENZAMIDE 65/119
8-METHOXYPSORALEN P/169
8-METHOXYPSORALEN 109/096
5-METHOXYPSORALEN 213/049
METHYL ACRYLATE 65/120
METHYL ACRYLATE 78/023
3-METHYLAMINO-4-METHYLPHENOL 73/244
METHYL AMYL KETONE P/181
2-METHYLBENZAMIDE 65/121
METHYL-2 BENZIMIDAZOLE CARBAMATE 73/245
4-(6-METHYL-2-BENZOTHIAZOLYL)-BENZENAMINE 73/246
4-(6-METHYL-2-BENZOTHIAZOLYL) BENZENAMINE 223/011
ALPHA-METHYLBENZYL ALCOHOL 83/067
ALPHA-METHYLBENZYL ALCOHOL 88/081
ALPHA-METHYLBENZYL ALCOHOL 109/097
METHYL BROMIDE P/148
METHYL BROMIDE P/180
METHYL BROMIDE 73/247
METHYL BROMIDE 109/098
METHYL BROMIDE 166/012
2-METHYL-2-BUTENENITRILE 65/123
2-METHYL-3-BUTENENITRILE 65/122
METHYL BUTYL KETONE P/151
METHYL CARBAMATE P/23
METHYL CARBAMATE P/149
METHYL CARBAMATE 65/124
METHYL CARBAMATE 79/031
METHYL CARBAMATE 83/068
METHYL CARBAMATE 109/099
METHYL CARBAMATE 167/016
METHYLCYCLOPENTADIENYL MANGANESE TRICARBONYL 213/050
METHYL DEMETON 73/248
N'-METHYL-N,N-DIPHENYLUREA 73/249
METHYLDOPA 65/125
METHYLDOPA 83/069
METHYLDOPA 88/082
METHYLDOPA 109/100
METHYL DOPA 232/005
METHYL DOPA 235/006
N,N'-METHYLENEBISACRYLAMIDE 66/126
4,4'-METHYLENEBIS(2-CHLOROANILINE) 66/127
4,4'-METHYLENEBIS(ORTHOCHLOROANILINE) P/151
METHYLENEBIS(4-CYCLOHEXYL ISOCYANATE) 73/250
2,2'-METHYLENE BIS(PHENYLENEOXY-METHYLENE)BISOXIRANE 73/251
METHYLENE BIS(THIOCYANATE) 73/252
METHYLENE BIS (THIOCYANATE) 222/016
METHYLENEDIANILINE 73/253
METHYLENE DIANILINE P/151
METHYL ETHYL KETONE P/151
METHYL ETHYL KETONE P/180
METHYLETHYL KETONE 73/254
METHYL ETHYL KETOXIME 213/051
METHYLGLUTARONITRILE 73/255
METHYL GLYCIDYL ETHER 73/256
METHYL ISOBUTYL KETONE 219/012

CHEMICAL PAGE/SEQ

METHYL MERCURIC CHLORIDE 73/257
METHYLMERCURY HYDROXIDE 73/258
METHYL METHACRYLATE 66/128
METHYL METHACRYLATE 81/057
METHYL METHACRYLATE 86/051
METHYL METHACRYLATE 110/101
2-METHYL-3-NITROANILINE 73/259
2-METHYL-4-NITROANILINE 73/260
2-METHYL-6-NITROANILINE 73/261
4-METHYL-2-NITROANILINE 73/262
4-METHYL-3-NITROANILINE 73/263
5-METHYL-2-NITROANILINE 73/264
N-METHYL-4-NITROANILINE 73/265
2-METHYL-3-NITRO-BENZOIC ACID 73/266
2-METHYL-5-NITROBENZOIC ACID 73/271
2-METHYL-6-NITROBENZOIC ACID 73/272
3-METHYL-2-NITRO-BENZOIC ACID 73/267
3-METHYL-4-NITRO-BENZOIC ACID 73/268
4-METHYL-3-NITRO-BENZOIC ACID 73/269
5-METHYL-2-NITRO-BENZOIC ACID 73/270
4-(N-METHYL-N-NITROSOAMINO)-1-(3-PYRIDYL)-1-BUTANONE 235/007
N-METHYL-N-NITROSOUREA P/54
N-METHYL-N-NITROSOUREA P/159
N-METHYLOLACRYLAMIDE 66/129
N-METHYLOLACRYLAMIDE 110/102
2-METHYLQUINOLINE 211/022
4-METHYLQUINOLINE 211/024
2-METHYLQUINOLINE HYDROCHLORIDE 211/023
4-METHYLQUINOLINE HYDROCHLORIDE 211/025
METHYL SALICYLATE 195/011
METHYL SALICYLATE 195/012
METHYL SALICYLATE 196/005
2-METHYLSTYRENE 213/052
METHYLTIN-TRIS(ISOOCTYLMERCAPTO-ACETATE) 73/273
METHYLTRIFLUOROMETHANESULFONATE 73/274
METHYL VIOLOGEN 83/070
METRONIDAZOLE 73/275
MEXACARBATE 73/276
MICHLER'S KETONE 74/277
MICHLER'S KETONE 86/052
MIN-U-SIL P/31
MIN-U-SIL P/125
MIN-U-SIL P/182
MIREX P/177
MIREX 86/053
MIREX 110/103
MIREX 165/008
MNNG/TPA/BPO (N-METHYL-N'-NITRO-N-NITR 116/013
MNNG/TPA/BPO (N-METHYL-N'-NITRO-N-NITR 116/014
MNNG/TPA/BPO (N-METHYL-N'-NITRO-N-NITR 116/015
MOLYBDENUM TRIOXIDE 74/278
MOLYBDENUM TRIOXIDE 83/071
MOLYBDENUM TRIOXIDE 86/054
MOLYBDENUM TRIOXIDE 166/013
MONENSIN 213/053
MONO-SEC-BUTANOLAMINE 63/029
MONOCHLOROACETIC ACID 79/008
MONOCHLOROACETIC ACID 80/019
MONOCHLOROACETIC ACID 106/026
MONOCYCLOHEXYLPHOSPHINE 212/029
MONOETHYL GLYCOL ETHER P/131
MONO(2-ETHYLHEXYL)ADIPATE 83/048
MONO(2-ETHYLHEXYL)ADIPATE 85/039
MONO(2-ETHYLHEXYL)PHTHALATE P/186
MONO(2-ETHYLHEXYL)PHTHALATE 78/024
MONO(2-ETHYLHEXYL)PHTHALATE 86/055
MONO(2-ETHYLHEXYL) PHTHALATE 197/022
MONO(2-ETHYLHEXYL)PHATHALATE 223/012
MONOISOPROPANOLAMINE 79/026
MONOSODIUM GLUTAMATE 74/279

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
MONOSODIUM METHANE ARSENATE	67/174
MONURON	P/44
MONURON	P/131
MUSK KETONE	66/130
NALIDIXIC ACID	66/131
NALIDIXIC ACID	81/058
NALIDIXIC ACID	88/083
NALIDIXIC ACID	110/104
NAPHTHALENE	110/105
4-(2-NAPHTHYLAMINO)PHENOL	74/280
ALPHA-NAPHTHYL ISOTHIOCYANATE	74/281
2-NAPHTHYL LACTATE	74/282
NAVY FUEL JP-5	163/021
NAVY FUELS JP-5	110/106
NEODECANOIC ACID, 2,3-EPOXYPROPYL ESTER	74/283
NEOPENTYL GLYCOL DIGLYCIDYL ETHER	74/284
NICKEL CARBONYL	74/285
NICKELOCENE	86/056
NICKEL OXIDE	114/019
NICKEL OXIDE	P/44
NICKEL SUBSULFIDE	115/021
NICKEL SULFATE	P/133
NICKEL SULFATE	P/230
NICKEL SULFATE HEXAHYDRATE	83/072
NICKEL SULFATE HEXAHYDRATE	114/020
NICOTINE PRECURSORS	235/008
NIFEDIPINE	74/286
M-NITROACETOPHENONE	66/132
O-NITROANILINE	66/134
P-NITROANILINE	66/133
P-NITROANILINE	78/026
P-NITROANILINE	110/107
P-NITROANILINE	166/014
O-NITROANISOLE	66/135
O-NITROANISOLE	110/108
9-NITROANTHRACENE	74/288
9-NITROANTHRACENE	86/057
9-NITROANTHRACENE	88/085
4-NITROANTHRANILIC ACID	88/086
M-NITROBENZAMIDE	66/136
O-NITROBENZAMIDE	66/138
P-NITROBENZAMIDE	66/137
NITROBENZENE	176/004
NITROBENZENE	234/005
4-NITRO-1,3-BENZENEDIAMINE	74/289
O-NITROBENZOIC ACID	74/290
M-NITROBENZOYL CHLORIDE	66/139
M-NITROBENZOYL CHLORIDE	223/013
O-NITROBENZOYL CHLORIDE	74/291
P-NITROBENZOYL CHLORIDE	88/087
P-NITROBENZOYL CHLORIDE	223/014
M-NITROBENZYL CHLORIDE	74/292
2-NITRO-1,1'-BIPHENYL	66/140
2-NITRO-1-BUTANOL	74/293
2-NITRODIPHENYLAMINE	74/294
2-NITROETHANOL	74/295
3-NITRO-9-FLUORENONE	74/296
3-NITRO-9-FLUORENONE	88/088
NITROFURANTOIN	83/073
NITROFURANTOIN	110/109
NITROFURAZONE	81/059
NITROFURAZONE	88/089
NITROFURAZONE	110/110
NITROFURAZONE	194/011
NITROFURAZONE	232/006
NITROGEN DIOXIDE	P/184
NITROGEN DIOXIDE IN NITROGEN	235/009
NITROMETHANE	222/017
1-NITRO-2-METHYLNAPHTHALENE	74/297
1-NITRO-2-METHYLNAPHTHALENE	86/058
1-NITRONAPHTHALENE	86/059

CHEMICAL	PAGE/SEQ
P-NITROPHENETHYL ALCOHOL	66/141
P-NITROPHENETHYL ALCOHOL ACETATE	74/298
O-NITROPHENETHYL ALCOHOL, ACETATE	74/299
M-NITROPHENOL	66/142
P-NITROPHENOL	110/111
P-NITROPHENOL	88/090
P-NITROPHENOL	116/016
(O-NITROPHENYL)ACETONITRILE	66/143
1-(4-NITROPHENYL)-2-CHLOROPROPANE	74/300
2-NITRO-P-PHENYLENEDIAMINE	74/301
4-NITRO-O-PHENYLENEDIAMINE	88/091
4-NITROPHTHALIC ANHYDRIDE	66/144
4-NITROPHTHALIC ANHYDRIDE	74/302
4-NITROPHTHALIMIDE	66/145
3-NITROPROPIONIC ACID	74/303
3-NITROPROPIONIC ACID	86/060
1-NITROPYRENE	74/304
1-NITROPYRENE	P/204
NITROSAMINES	P/126
NITROSAMINES	P/127
N-NITROSODIETHANOLAMINE	P/44
N-NITROSODIETHANOLAMINE	66/146
N-NITROSODIETHANOLAMINE	118/004
N-NITROSODIETHYLAMINE	74/305
N-NITROSODIMETHYLAMINE	66/147
N-NITROSODIMETHYLAMINE	78/027
N-NITROSODIMETHYLAMINE	235/010
N-NITROSODIPHENYLAMINE	74/306
N-NITROSO-N-ETHYLURETHANE	74/307
NITROSONORNICOTINE	235/011
4-NITROSOPHENOL	74/308
N-NITROSOPIPERIDINE	66/148
BETA-NITROSTYRENE	74/309
M-NITROTOLUENE	212/026
O-NITROTOLUENE	212/027
P-NITROTOLUENE	83/074
P-NITROTOLUENE	166/015
5-NITRO-O-TOLUIDINE	74/310
NONAMETHYLENEIMINE	74/311
NONYLPHENYL DIPHENYL PHOSPHATE (NPDPP MIXED ISOMERS)	74/312
NOREPINEPHRINE	P/137
NOSCAPINE	74/313
NOVACULITE	P/125
NTA(NITRILOTRIACETIC ACID)	74/287
NTA(NITRILOTRIACETIC ACID)	78/025
NTA(NITRILOTRIACETIC ACID)	88/084
OCHRATOXIN	P/156
OCHRATOXIN A	66/149
OCHRATOXIN A	110/112
OCHRATOXIN A	167/018
OCHRATOXIN A	167/017
OCTACHLORODIBENZODIOXIN	66/150
OCTACHLORONAPHTHALENE	74/314
OCTAMETHYLCYCLOTETRASILOXANE	218/004
OCTAMETHYLTRISILOXANE	219/005
OCTANOIC ACID	74/315
2-OCTYL-3-ISOTHIAZOLONE	74/316
N-OCTYL METHACRYLATE	66/151
P-N-OCTYLOXYBENZOIC ACID	74/317
OILS (VEGETABLE)	235/012
OLEIC ACID DIETHANOLAMINE	74/318
OLEIC ACID DIETHANOLAMINE	83/075
OLEIC ACID DIETHANOLAMINE	110/113
OLIVETOL	74/319
OLIVINE	P/125
ORDRAM	219/008
OXALIC ACID	196/037
OXALIC ACID	233/010
OXAZEPAM	210/010
OXETHAZAINE	66/152
4,4'-OXYDIANILINE	66/153

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
4,4'-OXYDIANILINE	86/061
OXYPHENBUTAZONE	213/054
OXYTETRACYCLINE HYDROCHLORIDE	79/032
OXYTETRACYCLINE HYDROCHLORIDE	81/060
OXYTETRACYCLINE HYDROCHLORIDE	83/076
OXYTETRACYCLINE HYDROCHLORIDE	110/114
PAPAVERINE.HCL	232/007
PENICILLIN V	81/061
PENICILLIN VK	86/062
PENICILLIN VK	110/115
PENTACHLOROANISOLE	81/062
PENTACHLOROANISOLE	110/116
PENTACHLOROETHANE	83/077
PENTACHLORONITROBENZENE	83/078
PENTACHLORONITROBENZENE	110/117
PENTACHLOROPHENOL, DOWICIDE EC-7	110/118
PENTACHLOROPHENOL, DOWICIDE EC-7	234/006
PENTACHLOROPHENOL(PCP)	176/003
PENTACHLOROPHENOL, TECHNICAL	110/119
PENTACHLOROPHENOL, TECHNICAL	234/007
PENTAERYTHRITOL TETRANITRATE	110/120
PENTAETHYLENEHEXAMINE	79/033
PENTAETHYLPENTAMINE	74/320
N-PENTANE	P/181
1-PENTANOL	P/181
1-PENTANOL	74/321
3-PENTANOL	P/181
3-PENTENENITRILE	74/322
2-PENTENENITRILE	75/323
2-(P-PENTYLPHENYL)-5-(P-PENTYL-OXYPHENYL) PYRIMIDINE	75/324
PERACETIC ACID	66/154
PERCHLOROMETHYL MERCAPTAN	75/325
PERMETHRIN	P/177
PERMETHRIN	P/178
PHENACETIN	81/063
PHENAMIPHOS	66/155
PHENANTHRENE	75/326
O-PHENANTHROLINE	86/063
PHENAZOPYRIDINE HYDROCHLORIDE	83/079
PHENESTERIN	79/034
PHENESTERIN	83/080
PHENETHYL ANTHRANILATE	66/156
M-PHENETIDINE	75/328
O-PHENETIDINE	66/157
P-PHENETIDINE	75/327
PHENIRAMINE MALEATE	86/064
PHENOBARBITAL	P/56
PHENOBARBITAL	P/159
PHENOBARBITAL	P/230
PHENOL	P/131
PHENOL	78/028
PHENOL	83/081
PHENOXY ACETIC ACID	81/064
PHENYLACETONITRILE	66/158
D-PHENYLALANINE	197/023
N-PHENYLBENZENAMINE	66/159
PHENYLBUTAZONE	81/065
PHENYLBUTAZONE	111/121
M-PHENYLENEDIAMINE	75/330
O-PHENYLENEDIAMINE	75/329
P-PHENYLENEDIAMINE DIHYDROCHLORIDE	75/331
P-PHENYLENEDIAMINE DIHYDROCHLORIDE	86/065
PHENYLEPHRINE HYDROCHLORIDE	81/066
PHENYLEPHRINE HYDROCHLORIDE	86/066
PHENYLEPHRINE HYDROCHLORIDE	111/122
2-PHENYL-2-ETHYLMALONDIAMIDE	66/160
PHENYL GLYCIDYL ETHER	75/332
1-PHENYL-3-METHYL-5-PYRAZOLONE	88/092
N-PHENYL-1-NAPHTHYLAMINE	75/333
N-PHENYL-2-NAPHTHYLAMINE	66/161
N-PHENYL-2-NAPHTHYLAMINE	111/123

CHEMICAL	PAGE/SEQ
O-PHENYLPHENOL	78/029
O-PHENYLPHENOL	81/067
O-PHENYLPHENOL	86/067
O-PHENYLPHENOL	111/124
O-PHENYLPHENOL	163/022
N-PHENYL-P-PHENYLENEDIAMINE	89/093
PHENYLPHOSPHINE	75/334
1-PHENYL-2-THIOUREA	89/094
PHENYTOIN (DIPHENYLHYDANTOIN)	111/125
PHENYTOIN (DIPHENYLHYDANTOIN)	117/015
PHOTODIELDRIN	89/095
PHTHALAMIDE	83/082
PHTHALAMIDE	89/096
PHTHALIC ANHYDRIDE	P/32
PHTHALIC ANHYDRIDE	P/183
PICLORAM	86/068
PICLORAM	217/012
PICRIC ACID	78/030
PICRIC ACID	89/097
PICRYL CHLORIDE	75/335
B-PINENE	222/018
PIPERONYL BUTOXIDE	P/131
POLYBROMINATED BIPHENYL MIXTURE (FIREMASTER FF-1)	P/96
POLYBROMINATED BIPHENYL MIXTURE (FIREMASTER FF-1)	111/126
POLYBROMINATED BIPHENYL MIXTURE (FIREMASTER FF-1)	117/016
POLYETHYLPOTASSIUM 2-BENZYL-4-CHLOROPHENATE	75/336
POLYTHIAZIDE	75/337
POTASSIUM P-TERT AMYLPHENATE	75/339
POTASSIUM CHLORIDE	83/083
POTASSIUM DICHROMATE	75/338
POTASSIUM FLUORIDE	81/068
PROBENECID	111/127
PROBENECID	197/024
PROBENECID	198/017
PROCARBAZINE HYDROCHLORIDE	75/341
PROGESTERONE	75/342
PROMETHAZINE HYDROCHLORIDE	66/162
PROMETHAZINE HYDROCHLORIDE	116/017
PROMETHAZINE HYDROCHLORIDE	166/016
1-PROPANOL	P/181
N-PROPANOL	P/190
N-PROPANOL	P/180
2-PROPANOL, 1-CHLORO-, PHOSPHATE (3:1)	75/343
PROPANOLS	P/193
PROPANTHELINE BROMIDE	66/163
PROPANTHELINE BROMIDE	166/017
PROPANTHELINE BROMIDE	196/011
PROPANTHELINE BROMIDE	233/011
PROPIONALDEHYDE	86/069
PROPIONALDEHYDE	198/018
PROPIONITRILE	66/164
2-PROPOXYETHANOL	197/025
S-(N-PROPYL)CHLOROTHIOFORMATE	P/203
S-(N-PROPYL)CHLOROTHIOFORMIC ACID	75/344
PROPYLENE	75/345
PROPYLENE	165/009
PROPYLENE CYANOHYDRIN	75/346
PROPYLENE GLYCOL	196/038
1,2-PROPYLENE GLYCOL	233/012
PROPYLENE GLYCOL MONOMETHYL ETHER	196/039
PROPYLENE GLYCOL MONOMETHYL ETHER	233/013
PROPYLENE OXIDE	P/50
PROPYLENE OXIDE	86/070
PROPYLENE OXIDE	89/098
PROPYLENE OXIDE	163/023
PROPYLENE OXIDE	165/010
1,3-PROPYLENE OXIDE	66/165
1,3-PROPYLENE OXIDE	89/099

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
PROPYL GALLATE	P/131
3-PROPYLIDENEPHTHALIDE	66/166
PSORALEN IV	166/018
PSORALENS	P/169
PYRENE	P/56
PYRENE	75/347
PYRIDINE	P/44
PYRIDINE	P/131
PYRIDINE	81/069
PYRIDINE	86/071
PYRIDINE	111/128
PYRIDINE	165/011
PYRILAMINE	P/119
PYRILAMINE	P/122
PYRILAMINE	104/013
PYRILAMINE	116/018
QUATERNARY AMMONIUM COMPOUNDS, BENZYL	67/167
QUERCETIN	111/129
QUERCETIN	167/019
QUERCETIN	167/020
QUINACRINE DIHYDROCHLORIDE	75/348
QUINACRINE MUSTARD	75/349
QUINETHAZONE (AQUAMOX)	75/350
QUINIDINE	67/168
QUINOLINE	78/031
QUINOLINE	83/084
QUINOLINE	86/072
RESCINNAMINE	75/351
RESERPINE	67/169
RESERPINE	79/035
RESORCINOL	79/036
RESORCINOL	81/070
RESORCINOL	111/130
RESORCINOL	111/131
RESORCINOL	117/017
13-CIS RETINOIC ACID	198/019
TRANS RETINOIC ACID	198/020
RHODAMINE 6G	81/071
RHODAMINE 6G	89/100
RHODAMINE 6G	111/132
RIDDELLINE	67/170
ROTENONE	P/121
ROTENONE	P/119
ROTENONE	83/085
ROTENONE	89/101
ROTENONE	111/133
ROTENONE	111/134
ROUNDUP	219/009
ROXARSONE	79/037
ROXARSONE	83/086
ROXARSONE	111/135
SAFROLE	P/56
SAFROLE	78/032
SAFROLE	81/072
SALICYLAZOSULFAPYRIDINE	67/171
SALICYLAZOSULFAPYRIDINE	115/022
SCOPOLAMINE HYDROBROMIDE	75/352
SCOPOLAMINE HYDROBROMIDE	115/023
SCOPOLAMINE HYDROBROMIDE	115/024
SCOPOLAMINE HYDROBROMIDE	232/008
SENECIPHYLLINE	67/172
SILICA	P/31
SILICA SAND	P/125
SODIUM ARSENILATE	67/173
SODIUM AZIDE	111/136
SODIUM BIFLUORIDE	81/073
SODIUM CHLORIDE	75/353
SODIUM CHLORIDE	81/074
SODIUM CHLORIDE	89/102
SODIUM CYANURATE	75/354
SODIUM CYCLAMATE	P/159
SODIUM CYCLAMATE	235/013
SODIUM DIETHYLDITHIOCARBAMATE	89/103
SODIUM DODECYL SULFATE	83/087
SODIUM DODECYL SULFATE	89/104
SODIUM DODECYL SULFATE	111/137
SODIUM DODECYL SULFATE	165/012
SODIUM DODECYL SULFATE	235/014
SODIUM FLUORIDE	81/075
SODIUM FLUORIDE	83/088
SODIUM FLUORIDE	86/073
SODIUM FLUORIDE	111/138
SODIUM FLUORIDE	116/019
SODIUM FLUORIDE	167/021
SODIUM IODOMETHANESULFONATE	75/355
SODIUM SACCHARIN	196/012
SODIUM XYLENESULFONATE	83/089
SODIUM XYLENESULFONATE	111/139
STANNOUS CHLORIDE	83/090
STANNOUS FLUORIDE	217/013
STANNOUS FLUORIDE	222/019
STEARATOCHROMIC CHLORIDE COMPLEX	75/356
STYRENE	75/357
STYRENE OXIDE	81/076
STYRENE OXIDE	118/005
STYRENE OXIDE	163/024
SUCCINIC ACID 2,2-DIMETHYLHYDRAZIDE	84/091
SUCCINIC ACID 2,2-DIMETHYLHYDRAZIDE	86/074
SUCCINIC ANHYDRIDE	67/175
SUCCINIC ANHYDRIDE	89/105
SUCCINIC ANHYDRIDE	111/140
SUCCINIC ANHYDRIDE	112/141
SUCCINONITRILE	67/176
SUCROSE	81/077
SUCROSE	83/092
SULFAMETHAZINE	P/33
SULFAMETHAZINE	P/122
SULFAMETHAZINE	P/152
SULFAMETHAZINE	P/153
SULFAMETHAZINE	112/142
SULFAMETHAZINE	117/018
SULFAMETHAZINE	194/006
SULFAMETHAZINE	195/013
SULFAMETHAZINE	196/013
SULFISOXAZOLE	P/131
SULFISOXAZOLE	75/358
3-SULFOLENE	89/106
4,4'-SULFONYLDIANILINE	83/093
SULFURYL FLUORIDE	P/180
TALC	112/143
TELONE II	101/012
TELONE II	102/013
TELONE II	P/44
TERGITOL NP-10	197/026
a-TERPINEOL	213/055
1,2,4,5-TETRABROMO-3,6-DIMETHYLBENZENE	75/359
1,2,4,5-TETRACHLOROBENZENE	222/020
1,2,4,5-TETRACHLOROBENZENE	P/135
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN	P/57
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN	P/142
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN	P/148
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN	P/156
2,3,7,8,-TETRACHLORODIBENZO-P-DIOXIN	P/161
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN	P/173
2,3,7,8-TETRACHLORODIBENZOFURAN	P/145
1,1,2,2-TETRACHLOROETHANE	78/033
1,1,2,2-TETRACHLOROETHANE	83/094
TETRACHLOROETHYLENE	P/44
TETRACHLOROETHYLENE	81/078
TETRACHLOROETHYLENE	83/095
TETRACHLOROETHYLENE	112/144
TETRACHLOROETHYLENE	112/145
TETRACHLOROETHYLENE	112/146
TETRACHLOROETHYLENE	112/147

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
TETRACHLOROETHYLENE	112/148
TETRACHLOROETHYLENE	112/149
TETRACHLOROETHYLENE	163/025
TETRACHLOROETHYLENE	165/013
TETRACHLOROETHYLENE	165/014
TETRACHLORONAPHTHALENE	75/360
2,3,5,6-TETRACHLORO-4-NITROANISOLE	75/361
2,3,5,6-TETRACHLORO-4-NITROANISOLE	83/096
2,3,5,6-TETRACHLORO-4-NITROANISOLE	89/107
2,3,4,5-TETRACHLOROPHENOL	75/363
2,3,4,6-TETRACHLOROPHENOL	75/362
2,3,4,6-TETRACHLOROPHENOL	219/010
2,3,5,6-TETRACHLOROPHENOL	75/364
TETRACHLOROPHTHALIC ANHYDRIDE	115/025
TETRACHLORVINPHOS	67/177
TETRACHROMIC ACID, POTASSIUM ZINC SALT	75/340
TETRACYCLINE HYDROCHLORIDE	79/038
TETRACYCLINE HYDROCHLORIDE	81/079
TETRACYCLINE HYDROCHLORIDE	89/108
TETRACYCLINE HYDROCHLORIDE	112/150
TETRADECANOIC ACID	75/365
TETRAETHYLDITHIOPYROPHOSPHATE	67/178
TETRAETHYLENEPENTAMINE	78/034
TETRAETHYLTHIURAM DISULFIDE	86/075
TETRAETHYLTHIURAM DISULFIDE (DISULFIRAM)	233/014
TETRAFLUOROETHYLENE	75/366
TETRAHYDROCANNABINOL	P/56
1-TRANS-DELTA-9-TETRAHYDROCANNABINOL	86/076
1-TRANS-DELTA-9-TETRAHYDROCANNABINOL	234/008
DELTA-9-TETRAHYDROCANNABINOL	P/173
TETRAHYDROFURAN	115/026
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM CHLORIDE	81/080
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM CHLORIDE	89/109
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM CHLORIDE	112/151
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM SULFATE	83/097
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM SULFATE	112/152
3,3',5,5'-TETRAMETHYLBENZIDINE	67/179
N,N,N',N'-TETRAMETHYL-P-PHENYLENEDIAMINE	75/367
TETRANITROMETHANE	112/153
1,3,6,8-TETRANITROPYRENE	75/368
1,3,6,8-TETRANITROPYRENE	P/204
THENYLDIAMINE	P/119
THENYLDIAMINE	P/120
THENYLDIAMINE	166/019
THEOBROMINE	195/014
THEOBROMINE	196/024
THEOPHYLLINE	67/180
THEOPHYLLINE	86/077
THEOPHYLLINE	194/007
THEOPHYLLINE	196/025
THEOPHYLLINE	232/009
THIABENDAZOLE	76/369
THIAZOLE	76/370
THIOACETAMIDE	76/371
4,4'-THIO-BIS(6-TERT-BUTYL-M-CRESOL)	P/147
4,4-THIOBIS(6-TERT-BUTYL-M-CRESOL)	86/078
4,4-THIOBIS(6-TERT-BUTYL-M-CRESOL)	104/014
4,4'-THIOBIS(6-T-BUTYL-M-CRESOL)	198/021
2,2'-THIOBIS(4,6-DICHLOROPHENOL)	67/181
4,4'-THIODIANILINE	67/182
THIOPHANATE M	76/372
THIOPHENE	222/021
THIOUREA	76/373
TITANIUM DIOXIDE	67/183
TITANIUM DIOXIDE	76/374

CHEMICAL	PAGE/SEQ
TITANIUM DIOXIDE	83/098
TITANIUM DIOXIDE	89/110
TITANOCENE DICHLORIDE	P/132
TITANOCENE DICHLORIDE	P/133
TITANOCENE DICHLORIDE	112/154
TITANOCENE DICHLORIDE	117/019
D-ALPHA-TOCOPHERYL ACETATE	P/129
D-ALPHA-TOCOPHERYL ACETATE	104/015
D-ALPHA-TOCOPHERYL SUCCINATE	76/375
D-ALPHA-TOCOPHERYL SUCCINATE	86/079
TOLAZAMIDE	76/376
TOLBUTAMIDE	89/111
O-TOLIDINE	140/010
O-TOLUALDEHYDE	76/377
TOLUENE	P/151
TOLUENE	P/170
TOLUENE	P/180
TOLUENE	P/184
TOLUENE (NITRATION GRADE)	89/112
TOLUENE (NITRATION GRADE)	112/155
TOLUENE (NITRATION GRADE)	117/020
TOLUENE (TECHNICAL)	81/081
TOLUENE (TECHNICAL)	89/113
2,6-TOLUENEDIAMINE DIHYDROCHLORIDE	76/378
2,6-TOLUENEDIAMINE DIHYDROCHLORIDE	83/099
2,5-TOLUENEDIAMINE SULFATE	76/379
2,5-TOLUENEDIAMINE SULFATE	89/114
TOLUENE DIISOCYANATE	165/015
TOLUENE ETHYLSULFONAMIDE	67/184
M-TOLUIDINE	76/380
ORTHO-TOLUIDINE	P/56
M-TOLUIDINE HYDROCHLORIDE	76/381
O-TOLUIDINE HYDROCHLORIDE	78/035
O-TOLUNITRILE	67/185
P-TOLUNITRILE	67/186
P-TOLUNITRILE	76/382
TOXICOLOGICAL INTERACTION-7 CHEMICAL MIXTURES	236/018
TRIALLYL ISOCYANURATE	76/383
TRIAMTERENE	112/156
TRIAMTERENE	166/020
1,3,5-TRICHLORO-1,3,5-TRIAZINE-2,4,6-(1H,3H,5H)-TRIONE	214/056
TRIBENZYL ISOCYANURATE	76/384
TRIBROMOACETONITRILE	76/385
2,4,6-TRIBROMOPHENYL CARBONATE	76/386
TRI-SEC-BUTANOLAMINE	76/387
TRI-N-BUTYLPHOSPHINE	212/030
TRICHLORFON	81/082
TRICHLORFON	89/115
TRICHLORFON	112/157
4,4,4-TRICHLORO-1,2-EPOXYBUTANE	67/187
1,1,2-TRICHLOROETHANE	67/188
1,1,1-TRICHLOROETHANE	163/026
1,1,1-TRICHLOROETHANE	165/016
1,1,1-TRICHLOROETHANE (METHYL CHLOROFORM	112/158
TRICHLOROETHYLENE	P/44
TRICHLOROETHYLENE	P/134
TRICHLOROETHYLENE	P/135
TRICHLOROETHYLENE	P/145
TRICHLOROETHYLENE	P/230
TRICHLOROETHYLENE	163/027
TRICHLOROETHYLENE	165/017
TRICHLOROETHYLENE	196/014
TRICHLOROETHYLENE	233/015
TRICHLOROETHYLENE	236/016
TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDR	104/016
TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDR	104/017

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDR	112/159
EPICHLOROHYDR	112/159
TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDR	112/160
TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDR	113/161
TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDR	113/162
TRICHLOROMELAMINE	76/388
2,3,4-TRICHLORONITROBENZENE	76/389
2,4,5-TRICHLORONITROBENZENE	76/390
2,4,6-TRICHLORONITROBENZENE	76/391
3,4,6-TRICHLORO-2-NITROPHENOL	76/392
2,3,4-TRICHLOROPHENOL	76/393
2,3,5-TRICHLOROPHENOL	76/394
2,3,6-TRICHLOROPHENOL	76/395
2,4,6-TRICHLOROPHENOL	P/131
3,4,5-TRICHLOROPHENOL	76/396
1,2,3-TRICHLOROPROPANE	166/021
TRICRESYL PHOSPHATE	115/027
TRICRESYL PHOSPHATE	115/028
TRICRESYL PHOSPHATE	166/022
TRICRESYL PHOSPHATE	196/015
TRICRESYL PHOSPHATE	233/016
TRIETHANOLAMINE	P/44
TRIETHANOLAMINE	115/029
TRIETHANOLAMINE	115/030
TRIETHANOLAMINE	115/031
TRIETHANOLAMINE	198/022
TRIETHYLENE GLYCOL	196/040
TRIETHYLENE GLYCOL DIACETATE	196/041
TRIETHYLENE GLYCOL DIACETATE	233/017
TRIETHYLENE GLYCOL DIGLYCIDYL ETHER	76/399
TRIETHYLENE GLYCOL DIMETHYL ETHER	194/008
TRIETHYLENE GLYCOL DIMETHYL ETHER	194/012
TRIETHYLENE GLYCOL DIMETHYL ETHER	196/042
TRIETHYLENE GLYCOL DIMETHYL ETHER	232/010
TRIETHYLENETETRAMINE	79/039
TRIFLUOROTHYMIDINE	76/400
1,8,9-TRIHYDROXYANTHRACENE	76/401
TRIMELLITIC ANHYDRIDE	104/018
TRIMELLITIC ANHYDRIDE	104/019
2,4,5-TRIMETHOXYBENZALDEHYDE	89/116
2,4,5-TRIMETHOXYBENZALDEHYDE	83/100
2,4,5-TRIMETHOXY-BENZALDEHYDE	198/023
TRIMETHYL ISOCYANURATE	76/402
TRIMETHYLTHIOUREA	83/101
TRIMETHYLTHIOUREA	89/117
TRIMETHYL TIN	P/178
TRIMETHYL TIN	P/179
2,4,6-TRINITROANILINE	76/403
1,3,6-TRINITROPYRENE	76/404
1,3,6-TRINITROPYRENE	P/204
2,4,6-TRINITROTOLUENE	76/405
TRIOCTANOIN	197/027
TRIOCTYLPHOSPHINE	212/031
TRIORTHOCRESYL PHOSPHATE	198/024
TRIPELENNAMINE	P/119
TRIPELENNAMINE	P/120
TRIPHENYLAMINE	67/189
TRIPELENNAMINE	116/020
TRIPELENNAMINE	166/023
TRIPHENYLANTIMONY	219/006
TRIPHENYLTIN HYDROXIDE	76/406
TRIPHENYLTIN HYDROXIDE	89/118
TRIPLENNAMINE	P/122
TRIPROLIDINE	P/119
TRIPROLIDINE	P/120
TRIPROLIDINE	P/122
TRIPROLIDINE	104/020
TRIPROLIDINE	116/021

CHEMICAL	PAGE/SEQ
TRI-N-PROPYLAMINE	76/407
TRIS(CARBAMOYLMETHYL)ISOCYANURATE	76/408
TRIS(2-CHLOROETHYL) PHOSPHATE	113/163
TRIS(2-CHLOROETHYL)PHOSPHATE	197/028
TRIS(2-CHLOROETHYL)PHOSPHITE	78/036
TRIS(3-CHLORO-2-HYDROXYPROPYL) ISOCYANURATE	76/409
TRIS(1,3-DICHLORO-2-PROPYL) PHOSPHATE	67/190
TRIS (2,3-EPOXYPROPYL) ISOCYANURATE	76/410
TRIS-(2-ETHYLHEXYL)PHOSPHATE	P/44
TRIS(2-ETHYLHEXYL)PHOSPHATE	P/186
TRIS(2-ETHYLHEXYL) PHOSPHATE	102/014
TRIS(2-ETHYLHEXYL)PHOSPHATE	165/018
TRIS(2-ETHYLHEXYL)TRIMELLITATE	76/411
1,3,5-TRIS(2-HYDROXYETHYL)TRIAZINE-2,4,6-TRIONE	76/412
TRIS(2-KETOPROPYL)ISOCYANURATE	76/413
TRIS(TRIPHENYLSTANNYL)ISOCYANURATE	76/414
O-TRITOLYL PHOSPHATE	76/398
P-TRITOLYL PHOSPHATE	76/397
TRITON X-100	197/029
TUMERIC OLEORESIN	166/024
TUMERIC, OLEORESIN (CURCUMIN)	113/164
TUNG OIL	214/057
TUNGSTEN CARBIDE	104/021
TUNGSTEN CARBIDE	P/183
TWEEN 60	197/030
URETHANE	P/54
URETHANE	P/56
URETHANE	P/124
URETHANE	77/415
UROTROPINE	67/191
VALERONITRILE	67/192
VANADIUM PENTOXIDE	P/32
VANADIUM PENTOXIDE	P/127
VANADIUM PENTOXIDE	P/137
VANADIUM PENTOXIDE	P/183
VANADIUM TRIOXIDE	P/137
VERAPAMIL	77/416
4-VINYLCYCLOHEXENE	83/102
4-VINYLCYCLOHEXENE	89/119
4-VINYLCYCLOHEXENE	113/165
4-VINYLCYCLOHEXENE	163/029
4-VINYLCYCLOHEXENE	163/028
VINYL CYCLOHEXENE DIEPOXIDE	81/083
VINYL CYCLOHEXENE DIEPOXIDE	113/166
VINYLCYCLOHEXENE DIEPOXIDE	P/173
1-VINYL-4-(DIETHYLDIAMINE)PIPERAZINE	77/417
VINYLIDENE CHLORIDE (1,1-DICHLOROETHYLENE)	83/103
VINYLIDENE CHLORIDE (1,1-DICHLOROETHYLENE)	89/120
VINYLIDENE FLUORIDE	77/418
VINYLIDENE FLUORIDE	89/121
VINYLIDENE FLUORIDE	166/025
VINYL TOLUENE	81/084
VINYL TOLUENE	89/122
VINYL TOLUENE	113/167
VITAMIN D	77/419
VITAMIN D	236/017
WATER	77/420
WATER	81/085
WATER	86/080
WITCH HAZEL (HAMAMELIS WATER)	P/44
WOLLASTONITE	P/161
WOLLASTONITE CALCIUM SILICATES	113/168
WOLLASTONITE CALCIUM SILICATES	118/021
XYLENE	163/030
XYLENE	P/151
XYLENES, COMMERCIAL MIXTURE	77/421
XYLENES, COMMERCIAL MIXTURE	113/169
2,4-XYLIDINE	67/193

ALPHABETIC INDEX TO TABLES

CHEMICAL	PAGE/SEQ
2,5-XYLIDINE	67/194
2,6-XYLIDINE	P/134
2,6-XYLIDINE	P/230
2,6-XYLIDINE	78/037
3,4-XYLIDINE	67/195
3,5-XYLIDINE	67/196
ZEOLITES	214/058
ZIRCONIUM SILICATES	P/125
ZIRCONOCENE DICHLORIDE	77/422

CAS REGISTRY NUMBER INDEX TO TABLES

CAS. NO.	PAGE/SEQ
50-00-0	65/092
50-00-0	78/018
50-00-0	198/013
50-06-6	P/56
50-06-6	P/159
50-06-6	P/230
50-18-0	87/036
50-29-3	P/177
50-29-3	P/178
50-29-3	236/015
50-32-8	P/48
50-32-8	P/56
50-32-8	P/57
50-32-8	P/125
50-32-8	79/003
50-32-8	87/009
50-33-9	81/065
50-33-9	111/121
50-34-0	66/163
50-34-0	166/017
50-34-0	196/011
50-34-0	233/011
50-44-2	P/54
50-55-5	67/169
50-55-5	79/035
50-71-5	68/009
50-78-2	68/003
50-81-7	82/005
51-03-6	P/131
51-17-2	69/051
51-19-4	210/002
51-28-5	71/168
51-34-3	115/023
51-34-3	115/024
51-34-3	232/008
51-41-2	P/137
51-43-4	64/077
51-78-5	210/005
51-79-6	P/54
51-79-6	P/56
51-79-6	P/124
51-79-6	77/415
52-28-8	64/046
52-28-8	85/022
52-53-9	77/416
52-68-6	81/082
52-68-6	89/115
52-68-6	112/157
53-96-3	P/48
53-96-3	P/56
53-96-3	P/135
54-31-9	83/052
54-31-9	108/076
55-18-5	P/159
55-18-5	74/305
55-21-0	63/017
55-31-2	108/064
55-31-2	167/009
55-66-9	197/024
56-23-5	P/43
56-23-5	P/145
56-23-5	P/180
56-23-5	69/078
56-53-1	P/56
56-53-1	80/035
56-53-1	85/026
56-53-1	195/006
56-53-1	195/007
56-53-1	196/002
56-53-1	235/003
56-54-2	67/168
56-72-4	70/104
56-72-4	82/025
56-72-4	87/035
56-93-9	63/022
57-06-7	P/149
57-06-7	82/002
57-41-0	P/96
57-41-0	P/172
57-41-0	P/178
57-41-0	111/125
57-41-0	117/015
57-50-1	81/077
57-50-1	83/092
57-55-6	196/038
57-55-6	233/012
57-63-6	72/186
57-66-9	111/127
57-66-9	198/017
57-68-1	P/33
57-68-1	P/122
57-68-1	P/152
57-68-1	P/153
57-68-1	112/142
57-68-1	117/018
57-68-1	194/006
57-68-1	195/013
57-68-1	196/013
57-74-9	85/018
57-83-0	75/342
57-97-6	78/013
57-97-6	116/008
57-97-6	116/009
57-97-6	116/010
58-08-2	P/119
58-08-2	P/120
58-08-2	166/005
58-08-2	195/002
58-08-2	195/003
58-08-2	196/001
58-08-2	196/023
58-25-3	210/007
58-33-3	66/162
58-33-3	116/017
58-33-3	166/016
58-54-8	64/078
58-55-9	67/180
58-55-9	86/077
58-55-9	194/007
58-55-9	196/025
58-55-9	232/009
58-89-9	P/177
58-89-9	P/178
58-90-2	75/362
58-90-2	219/010
58-93-5	81/051
58-93-5	109/086
58-93-5	167/014
58-93-5	194/005
58-94-6	69/091
58-95-7	P/129
58-95-7	104/015
59-87-0	81/059
59-87-0	88/089
59-87-0	110/110
59-87-0	194/011
59-87-0	232/006
60-11-7	71/145
60-13-9	79/002
60-13-9	105/006
60-57-1	88/050
61-25-6	232/007
61-76-7	81/066
61-76-7	86/066
61-76-7	111/122
61-82-5	68/038
61-82-5	80/003
61-82-5	82/003
61-82-5	87/005
62-44-2	81/063
62-50-0	P/48
62-50-0	P/51
62-50-0	P/57
62-53-3	80/005
62-55-5	76/371
62-56-6	76/373
62-73-7	P/48
62-73-7	70/129
62-73-7	80/031
62-73-7	85/023
62-73-7	107/050
62-75-9	P/190
62-75-9	P/192
62-75-9	66/147
62-75-9	78/027
62-75-9	235/010
64-17-5	P/56
64-17-5	P/180
64-17-5	P/190
64-17-5	196/028
64-17-5	233/005
64-18-6	221/013
64-69-7	72/225
64-75-5	79/038
64-75-5	81/079
64-75-5	89/108
64-75-5	112/150
64-77-7	89/111
65-85-0	69/053
66-71-7	86/063
66-81-9	70/111
67-20-9	83/073
67-20-9	110/109
67-56-1	P/180
67-56-1	P/190
67-63-0	P/180
67-63-0	P/190
67-64-1	P/180
67-64-1	198/002
67-66-3	P/135
67-66-3	P/184
67-66-3	163/007
67-68-5	71/158
67-72-1	83/055
67-72-1	109/083
68-12-2	P/124
68-12-2	P/127
68-12-2	80/037
68-12-2	88/055
69-05-6	75/348
69-65-8	83/061
70-00-8	76/400
70-25-7	116/013
70-25-7	116/014
70-25-7	116/015
71-23-8	P/180
71-23-8	P/181
71-23-8	P/190
71-36-3	P/180
71-41-0	P/181
71-41-0	74/321
71-43-2	P/44
71-43-2	P/50
71-43-2	P/56
71-43-2	P/170
71-43-2	80/007

CAS REGISTRY NUMBER INDEX TO TABLES

CAS. NO.	PAGE/SEQ	CAS. NO.	PAGE/SEQ	CAS. NO.	PAGE/SEQ
71-43-2	163/002	76-38-0	73/243	79-11-8	79/008
71-43-2	164/003	76-44-8	83/054	79-11-8	80/019
71-43-2	98/002	76-44-8	85/041	79-11-8	106/026
71-55-6	112/158	76-57-3	64/045	79-21-0	66/154
71-55-6	163/026	76-57-3	104/008	79-34-5	78/033
71-55-6	165/016	76-57-3	232/001	79-34-5	83/094
72-20-8	82/041	76-87-9	76/406	80-05-7	82/010
72-20-8	88/061	76-87-9	89/118	80-05-7	194/002
72-43-5	65/118	77-47-4	88/075	80-05-7	195/001
72-43-5	86/050	77-47-4	104/011	80-05-7	233/003
72-55-9	P/190	77-58-7	64/057	80-05-9	196/008
72-55-9	P/192	77-65-6	87/019	80-08-0	83/093
72-55-9	82/031	77-79-2	89/106	80-43-3	64/061
73-49-4	75/350	78-10-4	P/170	80-47-7	65/113
74-31-7	71/170	78-11-5	110/120	80-62-6	66/128
74-83-9	P/148	78-30-8	76/398	80-62-6	81/057
74-83-9	P/180	78-30-8	198/024	80-62-6	86/051
74-83-9	73/247	78-32-0	76/397	80-62-6	110/101
74-83-9	109/098	78-34-2	85/035	81-11-8	107/045
74-83-9	166/012	78-42-2	P/44	81-11-8	117/009
74-90-8	72/222	78-42-2	P/186	81-14-1	66/130
74-96-4	88/065	78-42-2	102/014	81-20-9	71/153
74-96-4	108/069	78-42-2	165/018	81-49-2	105/003
75-00-3	72/190	78-44-4	80/017	81-49-2	117/002
75-00-3	108/070	78-44-4	85/017	81-55-0	78/012
75-04-7	P/137	78-59-1	81/055	81-55-0	88/052
75-05-8	166/001	78-59-1	86/045	82-28-0	68/026
75-07-0	87/001	78-59-1	109/089	82-62-2	76/392
75-07-0	198/001	78-59-1	165/006	82-68-8	83/078
75-09-2	82/032	78-63-7	64/069	82-68-8	110/117
75-09-2	107/048	78-78-4	213/047	83-41-0	71/151
75-09-2	164/017	78-79-5	P/134	83-67-0	195/014
75-15-0	P/137	78-79-5	79/025	83-67-0	196/024
75-15-0	P/170	78-79-5	88/076	83-72-7	79/023
75-15-0	P/180	78-79-5	114/018	83-79-4	P/119
75-15-0	P/188	78-83-1	72/227	83-79-4	P/121
75-15-0	87/018	78-84-2	83/057	83-79-4	83/085
75-15-0	194/003	78-84-2	86/044	83-79-4	89/101
75-21-8	P/50	78-84-2	166/010	83-79-4	111/133
75-21-8	P/55	78-87-5	P/44	83-79-4	111/134
75-21-8	72/195	78-88-6	P/148	84-65-1	68/042
75-21-8	88/068	78-88-6	70/128	84-66-2	P/186
75-21-8	108/072	78-88-6	221/012	84-66-2	104/009
75-25-2	78/003	78-89-7	69/088	84-66-2	116/007
75-25-2	80/012	78-89-7	223/005	84-66-2	197/006
75-25-2	105/014	78-92-2	P/181	84-66-3	196/017
75-27-4	80/011	78-93-3	P/151	84-69-5	P/186
75-27-4	85/013	78-93-3	P/180	84-69-5	197/009
75-27-4	105/013	78-93-3	73/254	84-74-2	P/186
75-27-4	163/004	78-96-6	79/026	84-74-2	196/016
75-35-4	83/103	78-97-7	65/106	84-74-2	197/004
75-35-4	89/120	79-00-5	67/188	84-75-3	P/186
75-38-7	77/418	79-01-6	P/44	84-75-3	196/019
75-38-7	89/121	79-01-6	P/134	84-75-3	197/008
75-38-7	166/025	79-01-6	P/135	84-75-3	233/004
75-47-8	86/043	79-01-6	P/145	85-01-8	75/326
75-52-5	222/017	79-01-6	P/178	85-02-9	P/148
75-56-9	P/50	79-01-6	P/179	85-02-9	63/019
75-56-9	86/070	79-01-6	P/230	85-02-9	114/004
75-56-9	89/098	79-01-6	104/016	85-02-9	223/002
75-56-9	163/023	79-01-6	104/017	85-44-9	P/32
75-56-9	165/010	79-01-6	112/159	85-44-9	P/183
75-65-0	80/014	79-01-6	112/160	85-68-7	P/185
75-65-0	85/014	79-01-6	113/161	85-68-7	P/186
75-65-0	105/016	79-01-6	113/162	85-68-7	82/013
75-65-0	167/001	79-01-6	163/027	85-68-7	104/005
75-65-0	167/002	79-01-6	165/017	85-68-7	164/006
75-65-0	167/003	79-01-6	233/015	85-68-7	223/003
75-86-5	65/104	79-01-6	236/016	85-98-3	70/133
75-87-6	63/033	79-02-7	70/123	86-00-0	66/140
75-91-2	85/016	79-06-1	P/192	86-30-6	74/306
76-01-7	83/077	79-06-1	63/002	86-50-0	63/016

CAS REGISTRY NUMBER INDEX TO TABLES

CAS. NO.	PAGE/SEQ
86-57-7	86/059
86-72-6	69/077
87-08-1	81/061
87-29-6	64/043
87-29-6	80/025
87-62-7	P/134
87-62-7	P/230
87-62-7	78/037
87-68-3	P/130
87-68-3	P/143
87-68-3	114/014
87-68-5	176/003
87-86-5	110/118
87-86-5	110/119
87-86-5	234/006
87-86-5	234/007
88-06-2	P/131
88-21-1	68/015
88-23-3	68/022
88-72-2	212/027
88-73-4	210/011
88-74-4	66/134
88-88-0	75/335
88-89-1	78/030
88-89-1	89/097
88-96-0	83/082
88-96-0	89/096
89-25-8	88/092
89-40-7	66/145
89-58-7	71/156
89-62-3	73/262
89-63-4	82/020
89-69-0	76/390
89-87-2	71/154
90-30-2	75/333
90-41-5	63/023
90-43-7	78/029
90-43-7	81/067
90-43-7	86/067
90-43-7	111/124
90-43-7	163/022
90-45-9	196/006
90-94-8	74/277
90-94-8	86/052
91-08-7	64/067
91-17-8	197/003
91-20-3	110/105
91-22-5	78/031
91-22-5	83/084
91-22-5	86/072
91-23-6	66/135
91-23-6	110/108
91-63-4	211/022
91-64-5	78/008
91-64-5	107/042
91-68-9	70/132
91-79-2	P/119
91-79-2	P/120
91-79-2	166/019
91-80-5	P/119
91-80-5	104/012
91-80-5	116/012
91-80-5	118/003
91-81-6	P/119
91-81-6	P/120
91-81-6	P/122
91-81-6	116/020
91-81-6	166/023
91-84-9	P/119
91-84-9	P/122
91-84-9	104/013
91-84-9	116/018
91-93-0	P/131
92-36-4	73/246
92-36-4	223/011
92-59-1	65/089
92-87-5	P/23
92-87-5	P/57
92-87-5	P/138
92-87-5	P/172
92-87-5	P/173
92-87-5	140/001
92-87-5	176/005
93-05-0	70/138
93-43-6	74/282
93-45-8	74/280
93-46-9	71/159
94-20-2	87/032
94-36-0	63/020
94-59-7	P/56
94-59-7	78/032
94-59-7	81/072
94-70-2	66/157
95-50-1	82/030
95-50-1	164/015
95-53-4	P/56
95-54-5	75/329
95-55-6	210/001
95-64-7	67/195
95-68-1	67/193
95-76-1	64/058
95-78-3	67/194
95-79-4	82/022
95-83-0	63/037
95-84-1	68/027
95-85-2	68/021
95-94-3	P/135
95-94-3	222/020
96-09-3	81/076
96-09-3	118/005
96-09-3	163/024
96-12-8	P/54
96-12-8	P/55
96-12-8	P/129
96-12-8	64/054
96-12-8	87/041
96-12-8	195/004
96-12-8	196/009
96-13-9	P/169
96-13-9	80/029
96-13-9	107/046
96-18-4	166/021
96-23-1	70/127
96-24-2	63/038
96-29-7	213/051
96-33-3	65/120
96-33-3	78/023
96-45-7	P/96
96-45-7	78/017
96-45-7	83/047
96-45-7	108/073
96-45-7	117/012
96-48-0	87/016
96-48-0	105/019
96-67-3	68/033
96-69-5	P/147
96-69-5	86/078
96-69-5	104/014
96-69-5	198/021
96-91-3	68/024
96-93-5	68/034
96-98-0	73/269
97-02-9	P/150
97-02-9	71/160
97-02-9	78/014
97-02-9	88/057
97-18-7	67/181
97-32-5	65/119
97-53-0	P/44
97-53-0	79/018
97-77-8	P/124
97-77-8	86/075
97-77-8	197/013
97-77-8	233/014
98-00-0	213/044
98-01-1	81/045
98-01-1	108/075
98-01-1	198/014
98-11-3	69/050
98-30-6	68/030
98-37-3	68/035
98-55-5	213/055
98-56-6	219/011
98-83-9	213/052
98-85-1	83/067
98-85-1	88/081
98-85-1	109/097
98-88-4	P/44
98-88-4	69/056
98-95-3	176/004
98-95-3	234/005
99-01-6	196/014
99-07-0	64/068
99-08-1	212/026
99-12-7	71/155
99-30-9	70/122
99-30-9	78/010
99-51-4	71/152
99-52-5	73/260
99-54-7	87/046
99-55-8	74/310
99-56-9	88/091
99-57-0	80/002
99-57-0	105/004
99-82-1	65/112
99-98-9	71/157
99-99-0	83/074
99-99-0	166/015
100-00-5	210/012
100-01-6	66/133
100-01-6	78/026
100-01-6	110/107
100-01-6	166/014
100-02-7	88/090
100-02-7	110/111
100-02-7	116/016
100-15-2	73/265
100-22-1	75/367
100-27-6	66/141
100-40-3	83/102
100-40-3	89/119
100-40-3	113/165
100-40-3	163/028
100-40-3	163/029
100-41-4	P/134
100-41-4	P/151
100-41-4	P/170
100-41-4	64/083
100-41-4	85/038
100-42-5	75/357
100-44-7	63/021
100-44-7	80/010
100-44-7	87/010
100-44-7	118/001
100-47-0	63/018
100-47-0	114/003

BEST COPY AVAILABLE

CAS REGISTRY NUMBER INDEX TO TABLES

CAS. NO.	PAGE/SEQ
100-47-0	223/001
100-51-6	80/009
100-51-6	85/010
100-51-6	105/011
100-51-6	198/005
100-52-7	78/002
100-52-7	80/006
100-52-7	105/008
100-52-7	198/003
100-74-3	65/088
100-75-4	66/148
100-97-0	67/191
101-05-3	68/041
101-05-3	85/005
101-14-4	P/151
101-14-4	66/127
101-18-8	65/105
101-54-2	89/093
101-67-7	71/169
101-70-2	71/144
101-72-4	197/019
101-73-5	72/230
101-77-9	P/151
101-77-9	73/253
101-80-4	66/153
101-80-4	86/061
101-90-6	82/037
101-90-6	85/027
101-96-2	71/173
102-28-3	63/013
102-50-1	70/105
102-54-5	218/003
102-69-2	76/407
102-71-6	P/44
102-71-6	115/029
102-71-6	115/030
102-71-6	115/031
102-71-6	198/022
102-96-5	74/309
103-11-7	65/087
103-21-1	P/186
103-23-1	78/011
103-23-1	82/035
103-70-8	65/093
103-70-8	72/211
103-85-5	89/094
103-89-9	68/005
103-90-2	105/001
103-90-2	117/001
103-90-2	167/015
103-90-2	196/010
104-30-3	74/298
104-55-2	P/119
104-55-2	P/122
104-55-2	78/007
104-55-2	104/007
104-55-2	197/002
104-55-2	198/007
104-75-6	72/200
104-76-7	P/186
104-76-7	88/070
104-76-7	197/016
104-76-7	223/008
104-85-8	67/186
104-85-8	76/382
104-91-6	74/308
105-55-5	82/036
105-60-2	P/56
106-20-7	70/136
106-46-7	P/135
106-46-7	82/029
106-46-7	107/047
106-46-7	163/014
106-46-7	164/016
106-47-8	63/035
106-47-8	80/020
106-47-8	82/017
106-47-8	106/028
106-57-0	213/042
106-74-1	197/020
106-87-6	P/173
106-87-6	81/083
106-87-6	113/166
106-88-7	80/042
106-88-7	82/043
106-88-7	85/037
106-88-7	108/065
106-90-1	72/212
106-91-2	72/213
106-92-3	85/002
106-92-3	105/002
106-93-4	P/23
106-93-4	P/50
106-93-4	P/54
106-93-4	P/55
106-93-4	P/124
106-93-4	P/173
106-93-4	P/191
106-93-4	P/193
106-93-4	164/023
106-93-4	234/003
106-97-8	212/034
106-99-0	P/22
106-99-0	P/23
106-99-0	P/44
106-99-0	P/96
106-99-0	P/133
106-99-0	P/173
106-99-0	69/069
106-99-0	79/005
106-99-0	87/013
106-99-0	114/006
106-99-0	116/003
106-99-0	164/005
106-99-0	234/001
106-99-0	99/003
107-02-8	P/170
107-02-8	P/184
107-02-8	78/001
107-03-1	197/001
107-06-2	P/124
107-06-2	P/127
107-06-2	64/059
107-07-3	P/44
107-07-3	80/023
107-07-3	85/019
107-07-3	164/010
107-07-3	99/005
107-11-9	P/137
107-12-0	66/164
107-13-1	P/56
107-13-1	79/001
107-15-3	65/084
107-16-4	65/101
107-21-1	P/188
107-21-1	81/044
107-21-1	88/067
107-21-1	108/071
107-21-1	117/011
107-21-1	194/004
107-21-1	194/010
107-21-1	195/008
107-21-1	196/003
107-21-1	196/030
107-21-1	232/004
107-21-1	233/006
107-51-7	219/005
107-76-6	P/186
107-92-6	69/075
108-01-0	79/012
108-10-1	219/012
108-30-5	67/175
108-30-5	89/105
108-30-5	111/140
108-30-5	112/141
108-42-9	63/036
108-44-1	76/380
108-45-2	75/330
108-46-3	79/036
108-46-3	81/070
108-46-3	111/130
108-46-3	111/131
108-46-3	117/017
108-60-1	82/009
108-69-0	67/196
108-77-0	214/056
108-78-1	83/062
108-86-1	P/44
108-86-1	104/003
108-86-1	104/004
108-88-3	P/151
108-88-3	P/170
108-88-3	P/180
108-88-3	P/184
108-88-3	81/081
108-88-3	89/112
108-88-3	89/113
108-88-3	112/155
108-88-3	117/020
108-90-7	P/135
108-90-7	87/027
108-94-1	80/026
108-94-1	118/002
108-94-1	163/012
108-95-2	P/131
108-95-2	78/028
108-95-2	83/081
109-57-9	68/011
109-66-0	P/181
109-69-3	80/015
109-69-3	85/015
109-69-3	105/017
109-69-3	105/018
109-69-3	163/005
109-69-3	164/007
109-77-3	65/111
109-86-4	P/151
109-86-4	P/189
109-86-4	P/191
109-86-4	P/192
109-86-4	196/034
109-86-4	211/017
109-86-4	233/009
109-99-0	115/026
110-00-9	P/124
110-00-9	79/019
110-00-9	83/051
110-00-9	88/072
110-00-9	108/074
110-00-9	167/010
110-00-9	167/011
110-00-9	167/012
110-00-9	213/043
110-02-1	222/021
110-05-4	64/055
110-17-8	65/094

BEST COPY AVAILABLE

CAS REGISTRY NUMBER INDEX TO TABLES

CAS. NO.	PAGE/SEQ
110-21-4	69/064
110-21-4	87/012
110-26-9	66/126
110-43-0	P/181
110-49-6	P/170
110-49-6	211/018
110-54-3	P/151
110-54-3	P/180
110-59-8	67/192
110-61-2	67/176
110-77-0	197/018
110-80-5	P/131
110-80-5	P/151
110-80-5	P/170
110-80-5	P/190
110-80-5	P/191
110-80-5	82/045
110-80-5	108/068
110-80-5	163/018
110-80-5	164/024
110-80-5	195/009
110-80-5	211/015
110-86-1	P/44
110-86-1	P/131
110-86-1	81/069
110-86-1	86/071
110-86-1	111/128
110-86-1	165/011
111-15-9	P/190
111-15-9	196/033
111-15-9	211/016
111-21-7	233/017
111-27-3	P/181
111-30-8	78/019
111-30-8	81/046
111-30-8	108/078
111-30-8	164/025
111-30-8	198/015
111-35-3	197/015
111-35-3	198/012
111-41-1	79/022
111-42-2	82/034
111-42-2	88/051
111-42-2	107/052
111-42-2	198/010
111-44-4	79/004
111-46-6	196/026
111-69-3	68/006
111-76-2	P/151
111-76-2	P/170
111-76-2	P/190
111-76-2	196/031
111-76-2	211/013
111-76-2	233/007
111-77-3	P/190
111-90-0	P/170
111-90-0	P/190
111-90-0	196/027
111-90-0	196/032
111-96-6	P/151
111-96-6	194/009
111-96-6	232/002
112-07-2	211/014
112-24-3	79/039
112-27-6	196/040
112-49-2	194/008
112-49-2	194/012
112-49-2	196/042
112-49-2	232/010
112-56-1	69/070
112-56-1	220/004
112-57-2	78/034
113-92-8	82/023
113-92-8	87/031
113-92-8	106/033
114-49-8	75/352
114-83-0	63/001
115-07-1	75/345
115-07-1	165/009
115-09-3	73/257
115-28-6	80/018
115-28-6	87/024
115-28-6	106/024
115-28-6	163/006
115-96-8	113/163
115-96-8	197/028
116-06-3	68/008
116-06-3	85/001
116-14-3	75/366
117-08-8	115/025
117-39-5	111/129
117-39-5	167/019
117-39-5	167/020
117-81-7	P/56
117-81-7	P/185
117-81-7	P/186
117-81-7	80/034
117-81-7	85/025
117-81-7	164/019
117-81-7	195/005
117-81-7	196/018
117-81-7	197/007
117-81-7	235/002
117-84-0	196/020
117-84-0	197/012
118-52-5	P/144
118-52-5	197/005
118-71-8	79/028
118-74-1	88/074
118-92-3	85/006
118-96-7	76/405
119-15-3	64/071
119-31-3	71/146
119-32-4	73/263
119-34-6	63/014
119-36-8	195/011
119-36-8	195/012
119-36-8	196/005
119-53-9	P/56
119-75-5	74/294
119-84-6	116/006
119-90-4	P/23
119-90-4	P/138
119-90-4	P/139
119-90-4	P/230
119-90-4	107/054
119-90-4	117/010
119-90-4	140/003
119-90-4	167/008
119-93-7	P/23
119-93-7	P/138
119-93-7	P/139
119-93-7	P/230
119-93-7	107/056
119-93-7	140/010
120-32-1	P/148
120-32-1	104/002
120-32-1	116/001
120-32-1	116/002
120-32-1	166/003
120-37-6	64/081
120-40-1	65/110
120-40-1	83/058
120-40-1	109/090
120-61-6	88/056
120-71-8	70/106
120-80-9	212/037
120-83-2	80/030
120-83-2	107/049
121-14-2	88/059
121-19-7	79/037
121-19-7	83/086
121-19-7	111/135
121-47-1	68/016
121-54-0	P/44
121-54-0	85/009
121-54-0	114/002
121-54-0	198/004
121-57-3	68/017
121-59-5	69/076
121-66-4	P/131
121-69-7	80/036
121-69-7	88/054
121-69-7	107/055
121-75-5	83/060
121-75-5	217/011
121-79-9	P/131
121-88-0	105/005
121-89-1	66/132
121-90-4	66/139
121-90-4	223/013
122-04-3	88/087
122-04-3	223/014
122-39-4	66/159
122-59-8	81/064
122-60-1	75/332
122-62-3	213/041
122-80-5	63/012
122-99-6	196/035
123-05-7	72/197
123-30-8	63/015
123-30-8	210/004
123-31-9	79/021
123-31-9	81/052
123-31-9	109/087
123-38-6	86/069
123-38-6	198/018
123-72-8	198/006
123-72-8	114/008
123-72-8	114/009
123-77-3	P/149
123-77-3	85/007
123-77-3	114/001
123-88-6	73/242
123-91-1	82/039
124-07-2	74/315
124-09-4	114/015
124-48-1	P/44
124-48-1	164/009
124-48-1	99/004
124-64-1	81/080
124-64-1	89/109
124-64-1	112/151
126-07-8	72/214
126-27-2	66/152
126-31-8	75/355
126-98-7	65/117
126-98-7	79/030
126-99-8	P/134
126-99-8	87/030
127-00-4	69/087
127-00-4	79/009
127-00-4	223/004
127-18-4	P/44
127-18-4	81/078
127-18-4	83/095

CAS REGISTRY NUMBER INDEX TO TABLES

CAS. NO.	PAGE/SEQ
127-18-4	112/144
127-18-4	112/145
127-18-4	112/146
127-18-4	112/147
127-18-4	112/148
127-18-4	112/149
127-18-4	163/025
127-18-4	165/013
127-18-4	165/014
127-19-5	P/170
127-69-5	P/131
127-69-5	75/358
127-85-5	67/173
127-91-3	222/018
128-37-0	P/230
128-37-0	82/012
128-44-9	196/012
128-62-1	74/313
129-00-0	P/56
129-00-0	75/347
129-20-4	213/054
130-26-7	72/226
131-11-3	P/186
131-11-3	116/011
131-11-3	235/005
131-16-8	196/022
131-17-9	P/44
131-17-9	P/185
131-17-9	P/186
131-17-9	82/026
131-17-9	100/006
131-17-9	164/014
131-18-0	196/021
131-57-7	114/016
131-57-7	114/017
132-20-7	86/064
132-98-9	86/062
132-98-9	110/115
133-18-6	66/156
133-90-4	87/021
134-31-6	72/224
134-50-9	P/44
134-50-9	P/144
134-50-9	104/001
134-50-9	233/001
134-62-3	P/170
134-62-3	P/191
134-62-3	232/003
134-72-5	64/076
134-72-5	82/042
134-72-5	85/036
134-72-5	108/063
134-72-5	163/017
135-23-9	83/066
135-23-9	86/049
135-88-6	66/161
135-88-6	111/123
136-40-3	83/079
136-77-6	81/050
136-77-6	109/085
137-09-7	80/028
137-09-7	107/044
137-09-7	117/008
137-09-7	167/006
137-89-3	69/061
139-05-9	P/159
139-05-9	235/013
139-13-9	74/287
139-13-9	78/025
139-13-9	88/084
139-65-1	67/182
140-08-9	78/036
140-11-4	P/44
140-11-4	P/142
140-11-4	82/007
140-11-4	105/010
140-11-4	114/005
140-11-4	163/003
140-11-4	164/004
140-29-4	66/158
140-49-8	69/080
140-49-8	87/026
140-56-7	65/090
140-88-5	64/080
141-32-2	212/035
141-38-8	71/164
141-43-5	198/011
141-78-6	72/189
142-47-2	74/279
143-07-7	73/232
143-16-8	64/066
143-50-0	P/32
143-50-0	P/177
143-50-0	P/178
143-50-0	P/179
144-62-7	197/037
144-62-7	233/010
147-14-8	212/039
147-24-0	82/040
147-24-0	88/060
147-24-0	108/061
147-47-7	85/028
147-47-7	114/012
147-94-4	70/113
148-18-5	89/103
148-24-3	P/44
148-24-3	81/053
148-24-3	101/011
148-24-3	163/019
148-24-3	165/005
148-79-8	76/369
149-30-4	83/064
149-30-4	86/047
149-30-4	109/094
149-57-5	65/086
149-57-5	88/069
150-38-9	65/085
150-38-9	82/046
150-38-9	88/066
150-68-5	P/44
150-68-5	P/131
151-21-3	83/087
151-21-3	89/104
151-21-3	111/137
151-21-3	165/012
151-21-3	235/014
151-67-7	78/020
156-43-4	75/327
156-59-2	70/125
192-97-2	69/054
262-20-4	64/053
271-89-6	80/008
271-89-6	105/009
288-47-1	76/370
298-18-0	80/033
298-81-7	P/169
298-81-7	109/096
301-04-2	195/010
301-04-2	196/004
301-12-2	65/116
302-17-0	87/020
302-79-4	198/020
303-34-4	P/131
303-34-4	88/077
303-47-9	P/156
303-47-9	66/149
303-47-9	110/112
303-47-9	167/017
303-47-9	167/018
305-03-3	78/004
305-03-3	87/022
314-13-6	140/013
315-18-4	73/276
320-67-2	68/045
320-67-2	87/007
333-27-7	73/274
333-41-5	P/131
333-41-5	64/052
333-41-5	82/027
333-41-5	87/040
334-48-5	70/116
346-18-9	75/337
366-70-1	75/341
367-25-9	64/065
389-08-2	66/131
389-08-2	81/058
389-08-2	88/083
389-08-2	110/104
396-01-0	112/156
396-01-0	166/020
428-59-1	71/182
434-13-9	73/235
434-13-9	86/046
439-14-5	210/009
443-48-1	73/275
446-86-6	68/046
452-56-3	166/009
464-10-8	69/067
469-21-6	P/119
469-21-6	P/120
469-21-6	P/122
469-21-6	108/062
469-21-6	166/008
470-82-6	P/119
470-82-6	P/122
470-82-6	104/006
480-22-8	76/401
480-81-9	67/172
484-20-8	213/049
486-12-4	P/119
486-12-4	P/120
486-12-4	P/122
486-12-4	104/020
486-12-4	116/021
488-41-5	87/043
489-98-5	76/403
491-35-0	211/024
495-18-1	65/102
496-72-0	70/119
497-04-1	69/086
500-66-3	74/319
503-09-3	71/181
503-30-0	66/165
503-30-0	89/099
504-88-1	74/303
504-88-1	86/060
506-21-8	221/014
509-14-8	112/153
510-15-6	80/022
510-15-6	82/018
513-37-1	79/016
513-37-1	80/041
513-37-1	85/032
513-37-1	107/059
513-37-1	107/060
513-37-1	164/022

CAS REGISTRY NUMBER INDEX TO TABLES

CAS. NO.	PAGE/SEQ	CAS. NO.	PAGE/SEQ	CAS. NO.	PAGE/SEQ
513-37-1	176/002	591-78-6	P/151	686-68-0	71/141
518-47-8	P/44	594-42-3	75/325	752-74-9	76/414
520-18-3	213/048	594-71-8	69/085	756-79-6	79/013
521-31-3	73/236	597-25-1	79/014	756-79-6	80/039
521-31-3	216/010	597-25-1	80/040	756-79-6	107/057
521-31-3	221/015	597-25-1	85/031	756-79-6	163/016
527-62-8	68/023	597-25-1	107/058	756-79-6	197/011
527-85-5	65/121	597-25-1	164/021	759-73-9	P/51
529-19-1	67/185	598-55-0	P/23	759-73-9	P/53
529-20-4	76/377	598-55-0	P/149	759-73-9	P/54
532-27-4	106/027	598-55-0	65/124	759-94-4	72/194
532-27-4	167/004	598-55-0	79/031	759-94-4	78/016
532-28-5	65/103	598-55-0	83/068	768-52-5	65/108
532-82-1	79/010	598-55-0	109/099	822-68-4	212/029
536-33-4	64/079	598-55-0	167/016	827-16-7	76/402
536-33-4	72/187	599-79-1	67/171	828-00-2	85/029
537-92-8	68/004	599-79-1	115/022	828-00-2	107/053
538-23-8	197/027	600-25-9	69/084	828-00-2	167/007
540-51-2	63/026	602-38-0	71/166	829-84-5	212/028
542-75-6	P/44	602-60-8	74/288	833-43-2	74/299
542-75-6	P/44	602-60-8	86/057	839-90-7	76/412
542-75-6	88/049	602-60-8	88/085	842-07-9	P/131
542-75-6	101/012	603-34-9	67/189	842-07-9	63/042
542-75-6	102/013	603-36-1	219/006	868-85-9	80/038
542-75-6	164/018	603-54-3	71/171	868-85-9	85/030
542-78-9	P/44	603-83-8	73/259	868-85-9	100/007
542-78-9	109/092	604-75-1	210/010	868-85-9	164/020
542-78-9	163/020	605-71-0	71/167	881-03-8	74/297
542-78-9	165/007	605-71-0	85/034	881-03-8	86/058
542-78-9	198/016	606-03-1	76/384	920-66-1	72/218
544-63-8	75/365	606-37-1	71/165	924-42-5	66/129
548-62-9	P/33	609-19-8	76/396	924-42-5	110/102
548-62-9	P/119	609-31-4	74/293	930-22-3	71/176
548-62-9	P/121	610-14-0	74/291	930-37-0	73/256
548-62-9	P/122	610-15-1	66/138	933-75-5	76/395
548-62-9	P/152	610-66-2	66/143	933-78-8	76/394
548-62-9	P/153	611-06-3	88/047	934-32-7	68/018
548-62-9	78/022	612-82-8	71/148	935-95-5	75/364
548-62-9	108/077	613-13-8	87/004	961-11-5	67/177
548-62-9	109/084	614-45-9	P/143	982-57-0	79/007
551-06-4	74/281	614-45-9	87/015	989-38-8	81/071
552-16-9	74/290	614-45-9	114/007	989-38-8	89/100
552-30-7	104/018	614-95-9	74/307	989-38-8	111/132
552-30-7	104/019	616-23-9	64/060	992-59-6	P/92
554-84-7	66/142	619-17-0	88/086	992-59-6	140/015
555-30-6	65/125	619-23-8	74/292	998-40-3	212/030
555-30-6	83/069	619-80-7	66/137	999-55-3	63/011
555-30-6	88/082	621-31-8	64/082	999-81-5	87/028
555-30-6	109/100	621-33-0	75/328	1025-15-6	76/383
555-30-6	232/005	621-42-1	68/002	1047-16-1	P/204
555-30-6	235/006	623-30-3	65/095	1047-16-1	215/003
555-48-6	68/013	624-18-0	75/331	1047-16-1	220/006
556-52-5	65/096	624-18-0	86/065	1067-33-0	78/009
556-52-5	79/020	625-45-6	233/008	1067-33-0	82/028
556-52-5	81/047	625-48-9	74/295	1067-33-0	87/044
556-52-5	85/040	627-03-2	196/029	1072-52-2	87/008
556-52-5	108/079	627-30-5	69/089	1077-56-1	72/206
563-47-3	87/029	628-02-4	85/042	1116-54-7	P/44
563-47-3	106/030	636-21-5	78/035	1116-54-7	66/146
563-47-3	163/008	638-03-9	76/381	1116-54-7	118/004
563-47-3	164/011	638-21-1	75/334	1156-19-0	76/376
569-61-9	85/020	643-22-1	81/043	1163-19-5	P/145
569-61-9	106/036	643-22-1	88/064	1163-19-5	80/027
569-61-9	164/012	643-22-1	108/067	1163-19-5	87/038
570-24-1	73/261	645-09-0	66/136	1163-19-5	107/043
578-46-1	73/264	645-62-5	72/198	1163-19-5	163/013
583-39-1	P/144	656-67-2	218/004	1184-57-2	73/258
583-39-1	65/115	673-06-3	197/023	1185-81-5	64/056
583-39-1	83/063	680-31-9	P/54	1187-42-4	64/051
583-39-1	88/080	680-31-9	P/56	1189-85-1	69/071
584-02-1	P/181	684-93-5	P/54	1212-29-9	64/063
591-33-3	72/188	684-93-5	P/159	1212-29-9	80/032

CAS REGISTRY NUMBER INDEX TO TABLES

CAS. NO.	PAGE/SEQ
1212-29-9	82/033
1212-29-9	85/024
1260-17-9	69/079
1271-19-8	P/132
1271-19-8	P/133
1271-19-8	112/154
1271-19-8	117/019
1271-28-9	86/056
1277-43-6	70/103
1291-32-3	77/422
1295-35-8	69/059
1300-72-7	83/089
1300-72-7	111/139
1303-00-0	P/204
1303-00-0	219/013
1303-00-0	223/009
1309-37-1	P/125
1313-27-5	74/278
1313-27-5	83/071
1313-27-5	86/054
1313-27-5	166/013
1313-99-1	P/44
1313-99-1	114/019
1314-34-7	P/137
1314-62-1	P/32
1314-62-1	P/127
1314-62-1	P/137
1314-62-1	P/183
1314-87-0	P/137
1317-36-8	P/137
1318-02-1	214/058
1320-67-8	233/013
1325-37-7	P/44
1327-53-3	212/032
1330-20-7	P/151
1330-20-7	77/421
1330-20-7	113/169
1330-20-7	163/030
1330-78-5	115/027
1330-78-5	115/028
1330-78-5	166/022
1330-78-5	196/015
1330-78-5	233/016
1332-21-4	P/31
1332-21-4	P/156
1332-21-4	P/161
1335-87-1	72/217
1335-88-2	75/360
1338-23-4	80/013
1338-23-4	87/014
1338-23-4	105/015
1397-89-3	68/040
1406-16-2	77/419
1406-16-2	236/017
1420-04-8	70/102
1596-84-5	84/091
1596-84-5	86/074
1634-78-2	73/237
1675-54-3	85/011
1675-54-3	87/011
1719-53-5	70/134
1746-01-6	P/57
1746-01-6	P/142
1746-01-6	P/148
1746-01-6	P/156
1746-01-6	P/161
1746-01-6	P/173
1747-60-0	223/010
1759-58-6	71/149
1772-25-4	72/219
1825-21-4	81/062
1825-21-4	110/116
1843-48-7	76/408
1854-26-8	79/015
1854-26-8	104/010
1854-26-8	166/007
1897-45-6	82/021
1910-42-5	83/070
1912-24-9	68/044
1912-24-9	219/007
1918-02-1	86/068
1918-02-1	217/012
1936-15-8	P/131
1936-15-8	63/039
1937-37-7	P/92
1954-28-5	76/399
1972-08-3	P/56
1972-08-3	P/173
1972-08-3	86/076
1972-08-3	234/008
1975-50-4	73/266
1975-52-6	73/271
1982-37-2	166/011
2016-88-8	68/012
2039-87-4	69/090
2058-46-0	79/032
2058-46-0	81/060
2058-46-0	83/076
2058-46-0	110/114
2150-54-1	140/012
2157-01-9	66/151
2163-80-6	67/174
2164-17-2	65/091
2164-17-2	83/050
2185-92-4	P/131
2185-92-4	82/008
2210-79-9	70/107
2212-67-1	219/008
2212-81-9	69/058
2234-13-1	74/314
2244-16-8	105/020
2244-16-8	106/021
2335-64-8	221/011
2373-98-0	71/140
2385-85-5	P/177
2385-85-5	86/053
2385-85-5	110/103
2385-85-5	165/008
2404-44-6	71/177
2421-02-5	76/387
2425-79-8	79/006
2425-85-6	106/039
2425-85-6	117/006
2426-08-6	69/072
2429-71-2	140/005
2429-74-5	P/92
2429-74-5	P/138
2429-74-5	P/139
2429-74-5	106/037
2429-74-5	117/005
2429-74-5	140/007
2429-74-5	167/005
2432-99-7	P/131
2432-99-7	82/004
2438-88-2	75/361
2438-88-2	83/096
2438-88-2	89/107
2451-62-9	76/410
2461-15-6	72/201
2461-18-9	73/233
2475-45-8	63/041
2475-45-8	106/038
2475-45-8	163/011
2475-45-8	164/013
2489-77-2	83/101
2489-77-2	89/117
2493-84-7	74/317
2528-36-1	70/121
2567-01-3	75/346
2602-46-2	140/002
2610-10-8	P/204
2610-10-8	216/006
2610-10-8	221/009
2624-17-1	75/354
2675-77-6	69/083
2698-41-1	80/021
2698-41-1	106/029
2698-41-1	117/003
2699-79-8	P/180
2757-90-6	68/007
2783-94-0	72/208
2784-94-3	P/44
2784-94-3	81/049
2784-94-3	101/009
2784-94-3	165/002
2807-30-9	197/025
2832-40-8	P/31
2832-40-8	P/125
2832-40-8	P/127
2832-40-8	P/131
2835-39-4	85/003
2835-95-2	68/028
2836-00-2	68/029
2855-19-8	71/180
2871-01-4	65/098
2871-01-4	109/081
2871-01-4	165/004
2941-64-2	P/203
2941-64-2	72/191
3009-43-0	211/025
3018-12-0	67/045
3018-12-0	211/021
3039-13-2	70/120
3051-11-4	P/204
3051-11-4	216/007
3051-11-4	221/010
3083-23-6	78/015
3083-23-6	88/063
3083-25-8	67/187
3101-60-8	69/074
3113-71-1	73/268
3113-72-2	73/270
3118-97-6	72/207
3121-61-7	197/021
3129-91-7	64/062
3132-64-7	79/017
3209-22-1	88/048
3234-02-4	79/011
3234-28-4	72/185
3237-50-1	68/010
3237-50-1	87/003
3252-43-5	211/020
3266-23-7	71/175
3268-87-9	66/150
3296-90-0	P/169
3296-90-0	166/004
3296-90-0	196/007
3296-90-0	233/002
3319-31-1	76/411
3322-93-8	P/203
3322-93-8	P/204
3322-93-8	87/042
3546-10-9	79/034
3546-10-9	83/080
3567-69-9	87/034
3583-47-9	71/178

BEST COPY AVAILABLE

CAS REGISTRY NUMBER INDEX TO TABLES

CAS. NO.	PAGE/SEQ
3665-80-3	72/205
3687-22-7	71/164
3689-24-5	67/178
4016-14-2	79/027
4067-16-7	79/033
4080-31-3	69/081
4170-30-3	P/144
4170-30-3	114/010
4170-30-3	114/011
4170-30-3	198/009
4198-19-0	140/006
4206-61-5	70/135
4213-45-0	75/349
4337-65-9	83/048
4337-65-9	85/039
4342-03-4	64/048
4345-03-3	76/375
4345-03-3	86/079
4376-20-9	P/186
4376-20-9	78/024
4376-20-9	86/055
4376-20-9	197/022
4376-20-9	223/012
4396-27-4	74/311
4403-61-6	65/123
4444-68-2	64/064
4460-86-0	83/100
4460-86-0	89/116
4460-86-0	198/023
4553-62-2	73/255
4635-87-4	74/322
4731-53-7	212/031
4759-48-2	198/019
4823-47-6	63/027
4901-51-3	75/363
4914-30-1	70/117
5076-20-0	71/179
5089-96-3	P/178
5089-96-3	P/179
5124-30-1	73/250
5131-58-8	74/289
5160-02-1	P/131
5160-02-1	64/050
5307-14-2	74/301
5392-40-5	P/44
5392-40-5	85/021
5392-40-5	198/008
5397-31-9	72/203
5437-38-7	73/267
5466-84-2	66/144
5466-84-2	74/302
5470-11-1	72/223
5493-45-8	70/110
5522-43-0	P/204
5522-43-0	74/304
5610-64-0	P/31
5610-64-0	P/125
5610-64-0	P/127
5634-39-9	65/107
5634-39-9	81/054
5634-39-9	109/098
5660-60-6	70/101
5850-81-7	70/096
5850-90-8	70/099
5926-90-9	72/220
5989-27-5	83/059
5989-27-5	88/078
5989-27-5	109/091
6041-94-7	70/097
6201-86-1	68/037
6201-87-2	68/036
6219-89-2	68/025
6265-05-0	68/032
6265-06-1	68/031
6265-09-4	70/130
6265-11-8	71/147
6265-13-0	73/244
6265-15-2	68/014
6317-18-6	73/252
6317-18-6	222/016
6358-08-3	68/019
6358-09-4	68/020
6358-15-2	68/039
6358-18-5	69/082
6358-23-2	71/161
6358-29-8	140/016
6358-85-6	87/039
6369-59-1	76/379
6369-59-1	89/114
6373-74-6	63/040
6373-74-6	106/034
6375-17-3	68/001
6410-30-6	70/098
6428-94-0	64/075
6428-94-0	140/009
6459-94-5	P/138
6459-94-5	P/139
6459-94-5	78/006
6459-94-5	106/035
6459-94-5	117/004
6459-94-5	140/011
6471-49-4	106/040
6471-49-4	117/007
6537-68-4	73/234
6637-88-3	70/095
6637-88-3	140/014
6804-07-5	212/036
6959-48-4	78/005
6959-48-4	80/024
6959-48-4	82/019
7166-19-0	63/028
7177-48-2	80/004
7177-48-2	87/006
7177-48-2	105/007
7177-48-2	163/001
7177-48-2	164/001
7195-43-9	72/229
7320-37-8	82/044
7320-37-8	88/062
7320-37-8	108/066
7390-81-0	71/183
7423-53-2	76/409
7439-97-6	P/151
7440-38-2	P/127
7440-43-9	P/151
7440-48-4	P/183
7447-40-7	83/083
7487-94-7	P/132
7487-94-7	P/133
7487-94-7	79/029
7487-94-7	83/065
7487-94-7	86/048
7487-94-7	109/095
7487-94-7	117/014
7631-86-9	P/31
7647-14-5	75/353
7647-14-5	81/074
7647-14-5	89/102
7665-72-7	69/073
7673-09-8	76/388
7681-49-4	81/075
7681-49-4	83/088
7681-49-4	86/073
7681-49-4	111/138
7681-49-4	116/019
7681-49-4	167/021
7683-59-2	P/137
7705-08-0	83/049
7725-93-1	73/239
7732-18-5	77/420
7732-18-5	81/085
7732-18-5	86/080
7772-99-8	83/090
7778-50-9	75/338
7779-16-0	64/047
7783-06-4	P/137
7783-47-3	217/013
7783-47-3	222/019
7784-42-1	215/001
7784-42-1	220/002
7785-87-7	P/44
7785-87-7	109/093
7786-81-4	P/133
7786-81-4	P/230
7787-56-6	69/057
7789-23-3	81/068
8001-20-5	214/057
8001-79-4	63/032
8001-79-4	106/022
8003-22-3	P/204
8003-22-3	70/115
8003-22-3	216/009
8003-22-3	223/006
8008-20-6	110/106
8022-00-2	73/248
8024-37-1	113/164
8024-37-1	166/024
8047-99-2	67/184
8064-77-5	P/188
8064-77-5	194/001
9000-16-2	64/049
9002-93-1	197/029
9004-66-4	83/056
9005-65-6	108/080
9005-67-8	197/030
9016-45-9	197/026
10043-35-3	82/011
10043-35-3	85/012
10043-35-3	105/012
10101-97-0	83/072
10101-97-0	114/020
10102-44-0	P/184
10108-64-2	P/182
10108-64-2	82/014
10108-64-2	176/001
10108-64-2	234/002
10213-75-9	72/202
10277-43-7	73/231
10326-27-9	69/048
10326-27-9	82/006
10326-27-9	85/008
10326-27-9	166/002
10599-90-3	P/44
10599-90-3	106/023
10599-90-3	116/004
11024-24-1	71/139
11097-69-1	P/131
11097-69-1	68/043
12001-29-5	98/001
12001-29-5	164/002
12035-72-2	115/021
12070-12-1	P/183
12070-12-1	104/021
12083-48-6	69/060
12108-13-3	213/050
12433-50-0	75/340

CAS REGISTRY NUMBER INDEX TO TABLES

CAS. NO.	PAGE/SEQ
12715-61-6	P/204
12715-61-6	215/004
12715-61-6	221/007
12789-03-6	82/016
12789-03-6	87/023
13007-92-6	70/093
13007-92-6	87/033
13007-92-6	218/001
13042-18-7	72/209
13048-33-4	65/100
13098-39-0	65/099
13114-72-2	73/249
13284-42-9	75/323
13366-73-9	89/095
13463-39-3	74/285
13463-67-7	67/183
13463-67-7	76/374
13463-67-7	83/098
13463-67-7	89/110
13506-76-8	73/272
13530-68-2	220/005
13552-21-1	63/029
13674-84-5	75/343
13674-87-8	67/190
13684-63-4	73/241
13765-19-0	63/031
13765-19-0	80/016
13765-19-0	82/015
13765-19-0	87/017
13961-86-9	74/318
13961-86-9	83/075
13961-86-9	110/113
13983-17-0	113/168
13983-17-0	118/021
14097-03-1	P/204
14097-03-1	216/005
14097-03-1	221/008
14807-96-6	112/143
15110-74-4	71/162
15242-96-3	75/356
15356-70-4	65/114
15356-70-4	73/238
15481-70-6	76/378
15481-70-6	83/099
15791-78-3	70/100
15950-66-0	76/393
16091-18-2	64/073
16423-68-0	P/19
16529-56-9	65/122
16543-55-8	235/011
16561-29-8	213/045
17090-79-8	213/053
17341-40-1	64/070
17362-04-8	197/014
17369-59-4	66/166
17557-23-2	74/284
17700-09-3	76/389
17804-35-2	69/049
17901-16-5	70/126
18168-01-9	72/193
18708-70-8	76/391
19408-74-3	234/004
19686-73-8	69/068
20432-69-3	210/008
21739-91-3	70/114
21829-25-4	74/286
21838-75-5	71/172
22224-92-6	66/155
22839-37-0	212/033
23246-96-0	67/170
23255-93-8	72/221
23355-64-8	P/204
23355-64-8	216/008
23488-38-2	75/359
23564-05-8	76/372
24072-75-1	70/124
24072-75-1	223/007
24370-25-0	69/052
24382-04-5	81/056
24382-04-5	88/079
24815-24-5	75/351
25013-15-4	81/084
25013-15-4	89/122
25013-15-4	113/167
25155-25-3	69/062
25834-80-4	63/024
25843-45-2	69/047
25852-70-4	63/030
25869-00-5	72/210
25869-00-5	88/071
25869-00-5	218/002
25953-06-4	70/131
26227-73-6	73/240
26266-68-2	72/199
26401-97-8	64/072
26446-35-5	87/002
26471-62-5	165/015
26530-20-1	74/316
26628-22-8	111/136
26750-44-7	197/017
26761-40-0	P/186
26761-40-0	197/010
26761-45-5	74/283
26780-96-1	P/149
26780-96-1	114/013
27220-47-9	71/174
27556-51-0	69/055
28108-99-8	65/109
28109-00-4	71/142
28300-74-5	220/001
28322-02-3	P/56
28322-02-3	80/001
28322-02-3	82/001
28407-37-6	P/138
28407-37-6	P/139
28407-37-6	116/005
28407-37-6	140/008
28407-37-6	166/006
28767-61-5	P/204
28767-61-5	75/368
29671-57-6	72/204
29964-84-9	72/228
31551-45-8	71/163
31551-45-8	85/033
31551-45-8	88/058
33229-34-4	P/44
33229-34-4	65/097
33229-34-4	83/053
33229-34-4	101/010
33229-34-4	165/003
34197-98-3	74/300
34913-07-0	75/324
35065-27-1	P/146
35065-27-1	P/148
35471-49-9	75/336
38380-08-4	P/148
38411-22-2	P/146
38641-94-0	219/009
38848-76-9	71/150
39156-41-7	70/118
39817-09-9	73/251
42135-22-8	74/296
42135-22-8	88/088
42397-64-8	P/204
42397-65-9	P/204
50851-28-0	70/108
51207-31-9	P/145
51273-71-3	81/073
51990-12-6	106/031
51990-12-6	163/009
52417-22-8	85/004
52551-67-4	78/021
52551-67-4	88/073
52551-67-4	109/082
52551-67-4	117/013
52551-67-4	167/013
53404-18-5	75/339
54150-69-5	71/143
54150-69-5	82/038
54150-69-5	88/053
54289-46-2	70/137
54827-17-7	67/179
54849-38-6	73/273
55566-30-8	83/097
55566-30-8	112/152
56802-99-4	63/034
56802-99-4	87/025
56802-99-4	106/025
56802-99-4	164/008
57653-85-7	72/216
58139-59-6	69/063
59865-13-3	70/112
59865-13-3	87/037
61050-97-3	76/413
61578-04-9	70/109
61703-05-7	70/094
61703-05-7	140/004
61789-51-3	212/040
62763-89-7	211/023
63084-98-0	210/006
63449-39-8	106/032
63449-39-8	163/010
63449-39-8	212/038
63449-41-2	67/167
64216-20-2	63/025
64532-97-4	74/312
65646-68-6	213/046
67774-32-7	111/126
67774-32-7	117/016
67845-79-8	210/003
67990-32-3	76/386
68603-42-9	64/044
68603-42-9	82/024
68603-42-9	107/041
68916-39-2	P/44
68916-39-2	81/048
68916-39-2	100/008
68916-39-2	165/001
75321-19-6	P/204
75321-19-6	76/404
75321-20-9	P/204
75625-24-0	P/147
75625-24-0	72/215
80147-40-6	66/160
80789-74-8	79/024
83463-62-1	69/066
83463-62-1	211/019
89680-15-9	P/147
BROMOCHLOR	69/065
DIESELFUEL	107/051
EMTDP-1	63/003
EMTDP-2	63/004
EMTDP-3	63/005
EMTDP-4	63/006
EMTDP-5	63/007
EMTDP-6	63/008

CAS REGISTRY NUMBER INDEX TO TABLES

CAS. NO.	PAGE/SEQ
EMTDP-7	63/009
EMTDP-9	63/010
EMTDP-49	69/092
EMTDP-51	75/344
EMTDP-56	74/320
EMTDP-57	72/196
EMTDP-58	77/417
EMTDP-59	72/192
METHYL-2 B	73/245
TRIBROMOAC	76/385

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